

**SUBSTITUTED HETEROCYCLIC DERIVATIVES USEFUL AS  
ANTIDIABETIC AND ANTI-OBESITY AGENTS AND METHOD**

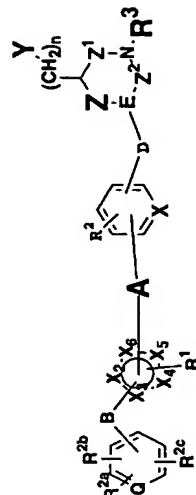
**Field of the Invention**

The present invention relates to novel substituted heterocyclic derivatives which modulate blood glucose levels, triglyceride levels, insulin levels and non-esterified fatty acid (NEFA) levels, and thus are particularly useful in the treatment of diabetes and obesity, and to a method for treating diabetes, especially Type 2 diabetes, as well as hyperglycemia, hyperinsulinemia, hyperlipidemia, obesity, atherosclerosis and related diseases employing such substituted acid derivatives alone or in combination with another antidiabetic agent and/or a hypolipidemic agent and/or other therapeutic agents.

**Description of the Invention**

In accordance with the present invention, substituted heterocyclic derivatives are provided which have the structure

I



A is  $(CH_2)_x$  where x is 1 to 5, or A is  $(CH_2)_x^1$ , where  $x^1$  is 1 to 5 with an alkenyl bond or an alkynyl bond embedded anywhere in the chain, or A is  $-(CH_2)_x^2-O-$   $(CH_2)_x^3$  where  $x^2$  is 0 to 5 and  $x^3$  is 0 to 5, provided that at least one of  $x^2$  and  $x^3$  is other than 0;

B is a bond or is  $(CH_2)_x^4$  where  $x^4$  is 1 to 5;

X is CH or N;

$X_2$  is C, N, O or S;

$X_3$  is C, N, O or S;

$X_4$  is C, N, O or S;

$X_5$  is C, N, O or S;

$X_6$  is C, N, O or S;

provided that at least one of  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$  and  $X_6$  is N; and at least one of  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$  and  $X_6$  is C.

In each of x through  $x_6$ , as defined above, C may include CH.

$R^1$  is H or alkyl;

$R^2$  is H, alkyl, alkoxy, halogen, amino, substituted

amino or cyano;

$R^{2a}$ ,  $R^{2b}$  and  $R^{2c}$  may be the same or different and are selected from H, alkyl, alkoxy, halogen, amino, substituted amino or cyano;

$R^3$  is selected from H, alkyl, arylalkyl,

aryloxy carbonyl, alkyl oxy carbonyl, alkynyl oxy carbonyl,

alkenyl oxy carbonyl, aryl carbonyl, alkyl carbonyl, aryl,

heteroaryl, cycloheteroalkyl, heteroaryl carbonyl,

heteroaryl-heteroarylalkyl, alkyl carbonyl amino,

heteroaryl oxy carbonyl, cycloheteroalkyl oxy carbonyl,

heteroarylalkyl, aminocarbonyl, substituted

aminocarbonyl, alkyl aminocarbonyl, aryl aminocarbonyl,

heteroarylalkenyl, cycloheteroalkyl-heteroarylalkyl;

hydroxyalkyl, alkoxy, alkoxyaryl oxy carbonyl,

arylalkyl oxy carbonyl, alkylaryl oxy carbonyl,

aryl heteroarylalkyl, arylalkylarylalkyl,

aryloxyarylalkyl, haloalkoxyaryl oxy carbonyl,

alkoxy carbonylaryl oxy carbonyl, aryloxyaryl oxy carbonyl,

arylsulfinylaryl carbonyl, arylthioaryl carbonyl,

alkoxy carbonylaryl oxy carbonyl, arylalkenyl oxy carbonyl,

heteroaryl oxy arylalkyl, aryloxyaryl carbonyl,

aryl carbonyl amino, heteroaryl carbonyl amino,

alkoxy carbonyl amino, aryloxy carbonyl amino,

heteroaryl oxy carbonyl amino, heteroaryl-

heteroaryl carbonyl, alkyl sulfonyl, alkyl sulfonyl,

heteroaryl oxy carbonyl, cycloheteroalkyl oxy carbonyl,

heteroarylalkyl, aminocarbonyl, substituted

aminocarbonyl, alkyl aminocarbonyl, aryl aminocarbonyl,

heteroarylalkenyl, cycloheteroalkyl-heteroarylalkyl;

hydroxyalkyl, alkoxy, alkoxyaryl oxy carbonyl,

arylalkyl oxy carbonyl, alkylaryl oxy carbonyl,

aryl heteroarylalkyl, arylalkylarylalkyl,

aryloxyarylalkyl, haloalkoxyaryl oxy carbonyl,

alkoxy carbonylaryl oxy carbonyl, aryloxyaryl oxy carbonyl,

arylsulfinylaryl carbonyl, arylthioaryl carbonyl,

alkoxy carbonylaryl oxy carbonyl, arylalkenyl oxy carbonyl,

heteroaryl oxy arylalkyl, aryloxyaryl carbonyl,

aryloxyarylalkyl oxy carbonyl, arylalkenyl oxy carbonyl,

arylalkyl carbonyl, aryloxyalkyl oxy carbonyl,

arylalkyl sulfonyl, arylthio carbonyl, arylalkenyl sulfonyl,

heteroaryl sulfonyl, aryl sulfonyl, alkoxyarylalkyl,

heteroarylalkoxy carbonyl, aryl heteroarylalkyl,

alkoxyaryl carbonyl, aryloxyheteroarylalkyl,

heteroarylalkyl oxy arylalkyl, arylarylalkyl,

arylalkenylarylalkyl, arylalkoxyarylalkyl,

aryl carbonylarylalkyl, alkylaryl oxy arylalkyl,

arylalkoxy carbonyl heteroarylalkyl, heteroarylarylalkyl,

aryl carbonyl heteroarylalkyl, heteroaryl oxy arylalkyl,

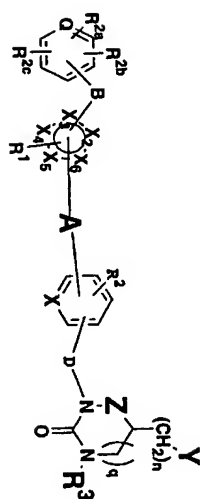
arylalkenyl heteroarylalkyl, aryl amino arylalkyl,

aminocarbonylarylalkyl;

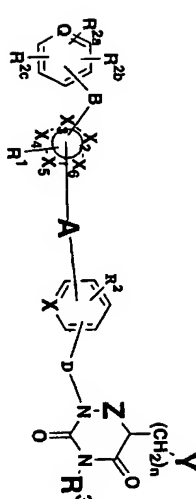
E is CH or N;



Ig



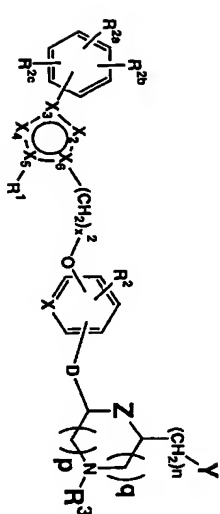
Ih



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Preferred are compounds of formula I of the invention having the structures IA and IB

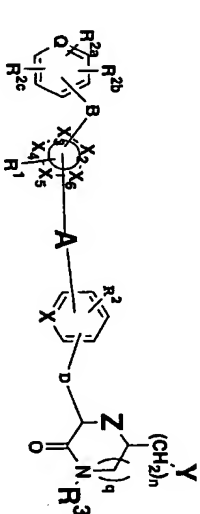
IA



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where X is CH.

IB



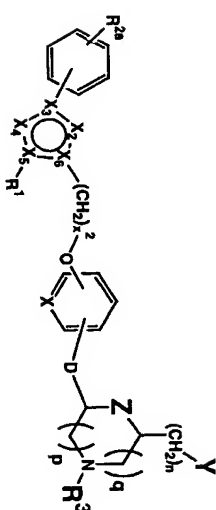
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where X is CH.

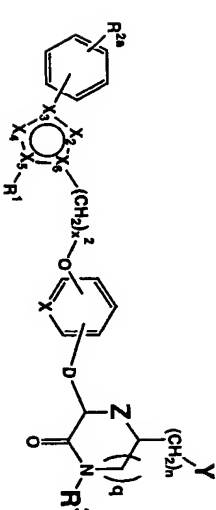
More preferred are compounds of formula I of the invention having the structures IC and ID

IC



10 where X = CH,

ID



15 where X is CH, q = 0, and Z is a single bond.

In the above compounds IC, it is most preferred that R<sup>1</sup> is alkyl, preferably CH<sub>3</sub>; R<sup>2a</sup> is alkyl, alkoxy or halogen, x<sup>3</sup> is 1 to 3; D is -CH= or (CH<sub>2</sub>)<sub>m</sub>, where m is 0 or (CH<sub>2</sub>)<sub>n</sub>, is CH<sub>2</sub> or CH-alkyl, X is CH, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub>, and X<sub>6</sub> represent a total of 1, 2 or 3 nitrogens; (CH<sub>2</sub>)<sub>n</sub> is a bond or CH<sub>2</sub>; p is 1; Z is a bond, q is 1; R<sup>3</sup> is alkoxy/carbonyl, aryl, heteroaryl, aryloxy/carbonyl or arylalkyl; Y is CO<sub>2</sub>R<sup>4</sup>; and n is 0.

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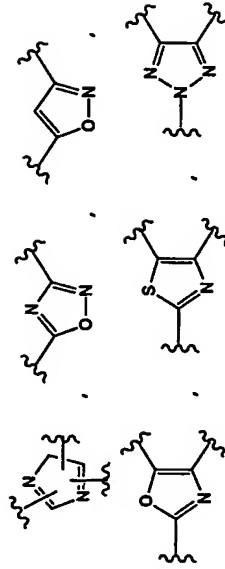


In the above compounds ID, it is most preferred that R' is alkyl, preferably CH<sub>3</sub>; R" is alkyl, alkoxy or halogen, x' is 1 to 3; D is -CH= or (CH<sub>2</sub>)<sub>m</sub> where m is 0 or (CH<sub>2</sub>)<sub>n</sub> is CH<sub>2</sub> or CH-alkyl, X is CH, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, and X<sub>5</sub> represent a total of 1, 2 or 3 nitrogens; (CH<sub>2</sub>)<sub>n</sub> is a bond or CH<sub>2</sub>; Z is a bond, q is 0 or 1; R' is alkoxycarbonyl, aryl, heteroaryl, aryloxy, carbonyl or arylalkyl; Y is CO<sub>2</sub>R'; and n is 0.

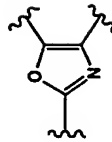
# 10 Examples of



groups present in the compounds of the invention include, but are not limited to

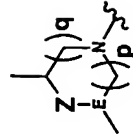


as well as those five-membered rings covered under the definition of heteroaryl set out hereafter,

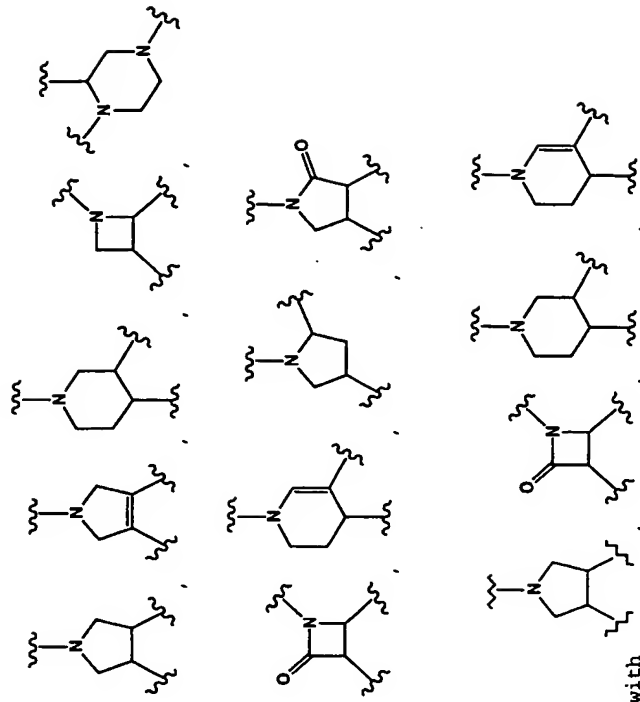


with being preferred.

# Examples of

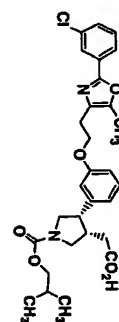
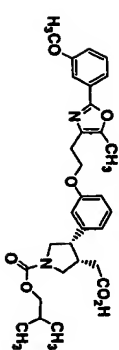
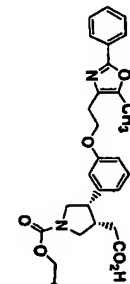
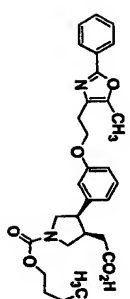
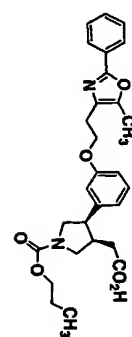
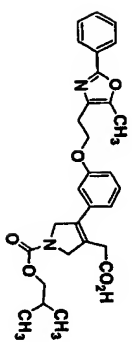


which may be present in the compounds of the invention include, but are not limited to

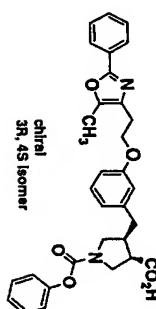
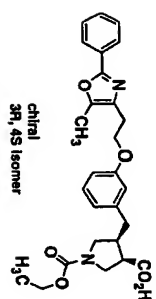
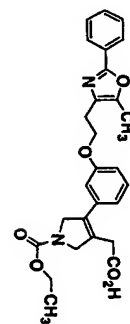
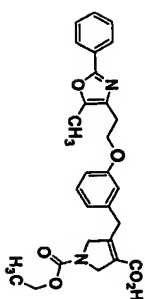


being preferred.

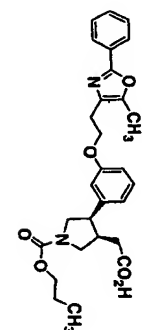
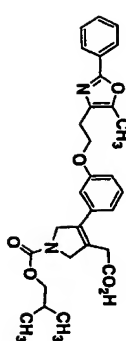
Preferred compounds of the invention include the following:



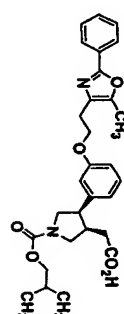
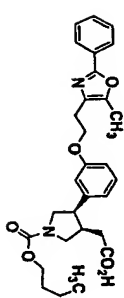
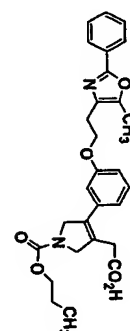
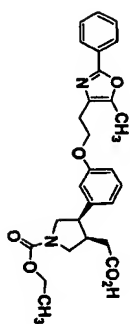
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chiral  
3R, 4S isomerchiral  
3R, 4S isomer

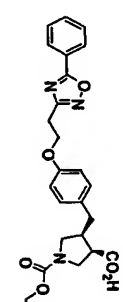
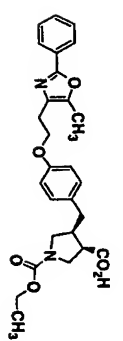
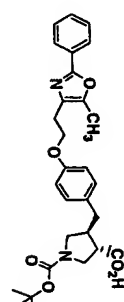
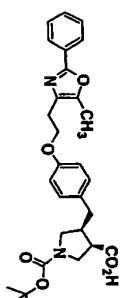
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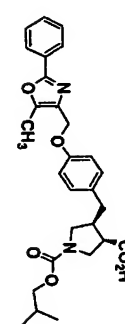
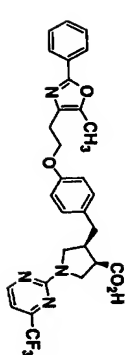
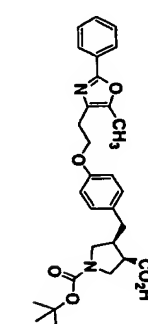
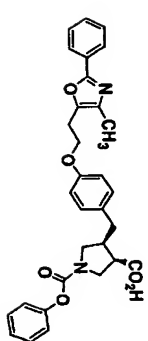
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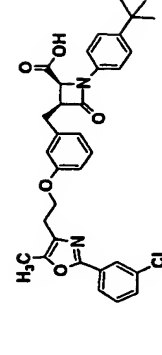
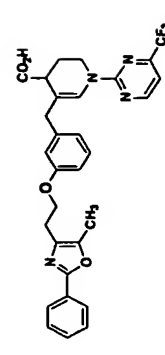
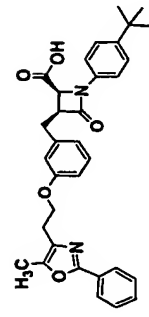
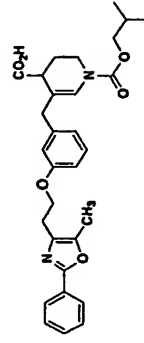
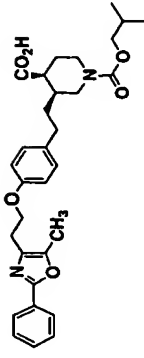
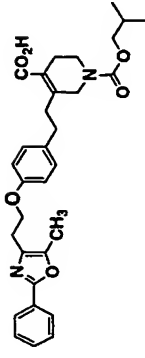
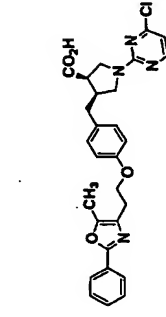
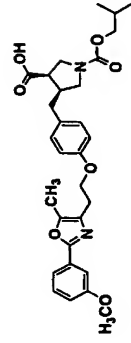
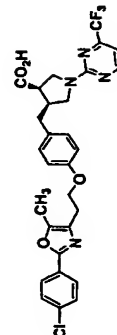
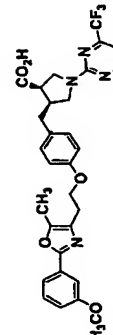
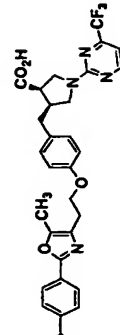
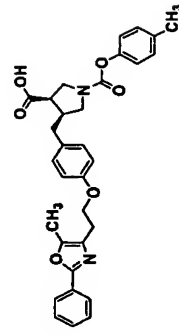
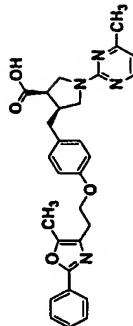
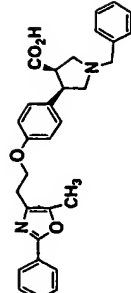
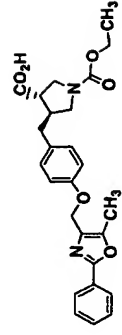
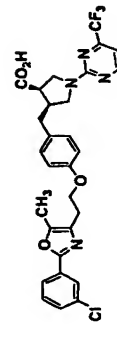
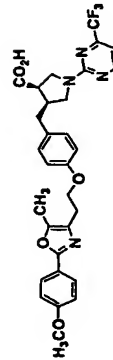
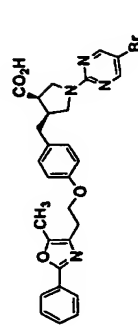
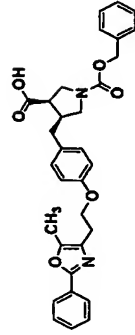
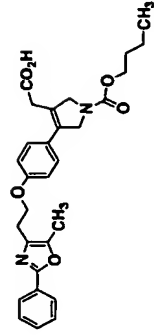
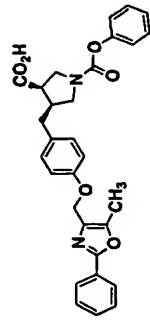
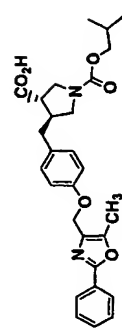


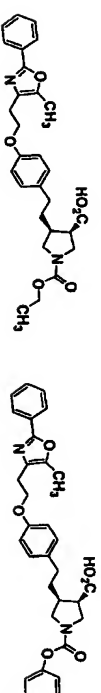
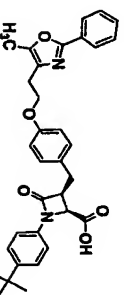
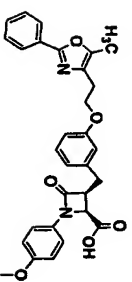
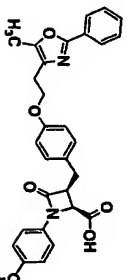
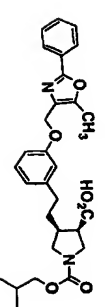
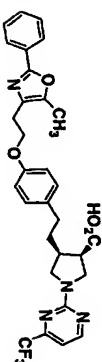
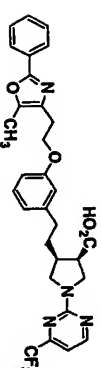
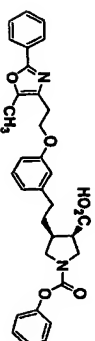
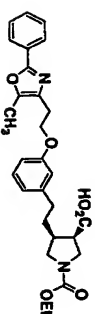
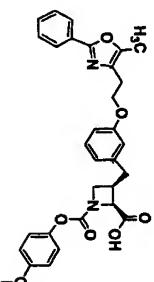
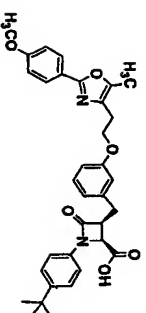
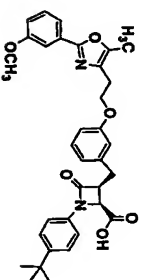
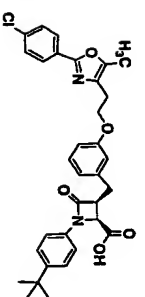
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In addition, in accordance with the present

invention, a method is provided for treating diabetes, especially Type 2 diabetes, and related diseases such as Type 1 diabetes, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, inflammation, Syndrome X, diabetic complications, dysmetabolic syndrome, atherosclerosis, and related diseases wherein a therapeutically effective amount of a compound of structure I is administered to a patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating early malignant lesions (such as ductal carcinoma in situ of the breast and lobular carcinoma in situ of the breast), premalignant lesions (such as fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN), liposarcomas and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and osteoporosis and proliferative diseases such as psoriasis, wherein a therapeutically effective amount of a compound of structure I is administered to a patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating diabetes and related diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of structure I and another type antidiabetic agent and/or a hypolipidemic agent, and/or lipid modulating agent and/or other type of therapeutic

agent, is administered to a human patient in need of treatment.

In the above method of the invention, the compound of structure I will be employed in a weight ratio to the antidiabetic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 10:1.

The conditions, diseases, and maladies

collectively referenced to as "Syndrome X" or Dysmetabolic Syndrome (as detailed in Johanson, *J. Clin. Endocrinol. Metab.*, 1997, 82, 727-734, and other publications) include hyperglycemia and/or prediabetic insulin resistance syndrome, and is characterized by an initial insulin resistant state generating

hyperinsulinemia, dyslipidemia, and impaired glucose tolerance, which can progress to Type II diabetes, characterized by hyperglycemia, which can progress to diabetic complications.

The term "diabetes and related diseases" refers to Type II diabetes, Type I diabetes, impaired glucose tolerance, obesity, hyperglycemia, Syndrome X, dysmetabolic syndrome, diabetic complications and hyperinsulinemia.

The conditions, diseases and maladies collectively referred to as "diabetic complications" include retinopathy, neuropathy and nephropathy, and other known complications of diabetes.

The term "other type(s) of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than compounds of formula I), one or more anti-obesity agents, and/or one or more lipid-lowering agents, one or more lipid modulating agents (including anti-atherosclerosis agents), and/or one or more antiplatelet agents, one or more agents for treating hypertension, one or more anti-cancer drugs, one or more agents for treating arthritis, one or more anti-osteoporosis agents, one or more anti-obesity agents, one or more agents for

treating immunomodulatory diseases, and/or one or more agents for treating anorexia nervosa.

The term "lipid-modulating" agent as employed herein refers to agents which lower LDL and/or raise HDL and/or lower triglycerides and/or lower total cholesterol and/or other known mechanisms for therapeutically treating lipid disorders.

# Detailed Description of the Invention

The compounds of the formula I of the present invention may be prepared according to the following general synthetic schemes, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples. Protection and deprotection in the Schemes below may be carried out by procedures generally known in the art (see, for example, Greene, T. W. and Wuts, P. G. M., *Protecting Groups in Organic Synthesis*, 3<sup>rd</sup> Edition, 1999 [Wiley]).

The synthesis of some key intermediates required for the synthesis of the compounds in this patent are described in Scheme 1. An alcohol 1 ( $R^1(CH_2)_2OH$ ) (which preferably is 2-phenyl-5-methyl-oxazole-4-ethanol) is coupled with a hydroxy aryl- or heteroaryl-aldehyde 2 under standard Mitsunobu reaction conditions (e.g. Mitsunobu, O., *Synthesis*, 1981, 1) to furnish the key intermediate aldehyde 3. Alternatively, the alcohol 1

can be converted to its methanesulfonate ester 4 under standard conditions; the mesylate 4 can then be used to alkylate the hydroxy aryl- or heteroaryl-aldehyde 2 to furnish the aldehyde 3.

A synthesis of the pyrrolidine acids I is shown in Scheme 2. Treatment of the aldehyde 3 with the Horner-Emmons reagent  $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$  5 (W. C. Still et

al., *Tetrahedron Lett.* **1985**, *24*, 4405-5508) provides the 2-alkenyl ester 6. This 2-alkenyl ester 6 is then reacted with N-trimethylsilylmethyl N-methoxymethyl benzylamine 7 under standard literature conditions (e.g. J. S. Carey, *J. Org. Chem.*, **2001**, *66*, 2526-2529) to give the corresponding N-benzyl pyrrolidine-ester 8.

Deprotection of the N-benzyl group (hydrogenation) gives the key intermediate, pyrrolidine-ester 9. Reaction of pyrrolidine 9 with chloroformate 10

( $\text{R}^6\text{O}-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-\text{Cl}$  where  $\text{R}^6$  is any of the  $\text{R}^3$  groups except H) provides the pyrrolidine-carbamate ester 11. Deprotection of the ester 11 then furnishes the cis-substituted pyrrolidine-carbamate acids I of the invention.

Scheme 3 shows the synthesis of other analogs from the key intermediate pyrrolidine-ester 9. Palladium-mediated reaction of 9 with aryl or heteroaryl bromides (e.g. method of Buchwald et. al., *J. Am. Chem. Soc.*, **2001**, *123*, 7727) furnishes the N-aryl or N-heteroaryl pyrrolidine acids II of the invention. Reductive amination of 9 (e.g. the procedure of Abdel-Magid et al, *J. Org. Chem.* **1996**, *61*, 3849) with appropriate aldehydes  $\text{R}^3\text{CHO}$  provides the substituted alkyl pyrrolidine acids III of the invention. Treatment of 9 with diverse acid chlorides  $\text{R}^3\text{COCl}$  in the presence of an appropriate base gives the corresponding amide pyrrolidine acids IV of the invention. Reaction of 9 with diverse isocyanate  $\text{R}^3\text{N}=\text{C}=\text{O}$  provides the corresponding urea pyrrolidine acids V of the invention. Treatment of 9 with sulfonyl chlorides  $\text{R}^3\text{SO}_2\text{Cl}$  furnishes the corresponding sulfonamide pyrrolidine acids VI of the invention. It is understood that these representative reactions of pyrrolidine 9 shown in Scheme 3 are also readily applied to the subsequent key secondary amine intermediates described below to give the corresponding functionalized analogs.

A synthesis of the homologated cis-substituted pyrrolidine acids VII of the invention is shown in Scheme 4. Treatment of aldehyde 3 with a substituted

alkynylmetal agent (generated from alkynes 12 in the presence of an appropriate base, e.g. n-butyllithium) furnishes the acetylenic alcohol adduct 13. Alcohol 13 is deoxygenated under standard methods (e.g.  $\text{Et}_3\text{SiH}/\text{H}_2/\text{Lindlar's catalyst}$ ) to give the 2-alkenyl ester 15. This 2-alkenyl unsaturated ester 15 is then reacted with

N-trimethylsilylmethyl N-methoxymethyl benzylamine 7 under standard literature conditions (J. S. Carey, *J. Org. Chem.*, **2001**, *66*, 2526-2529) to give the corresponding N-benzyl pyrrolidine-ester 16.

Deprotection of the N-benzyl group (hydrogenation) gives the key intermediate, pyrrolidine-ester 17. Reaction of pyrrolidine 17 with chloroformate 10 provides pyrrolidine-carbamate ester 18. Deprotection of the ester 18 then provides the cis-substituted pyrrolidine-carbamate acids VII of the invention.

An alternative synthesis of the key intermediate pyrrolidine ester 17 (for the special case where  $m = 0$ ) is shown in Scheme 4A. Alcohol 13 is acetylated under standard conditions to give the acetylenic acetate 13A, which is then reacted with N-trimethylsilylmethyl N-methoxymethyl benzylamine 7 under standard literature conditions (e.g. J. S. Carey, *J. Org. Chem.*, **2001**, *66*, 2526-2529) to give the N-benzyl dihydropyrrole 16A.

Exhaustive hydrogenation/ hydrogenolysis of the benzylic acetate, the dihydropyrrole and the N-benzyl group then provides the intermediate pyrrolidine-ester 17.

Scheme 5 illustrates a synthetic route to the corresponding trans-substituted pyrrolidine-carbamate acids VIII of the invention. Aldehyde 3 undergoes a Wittig reaction with a phosphoranylidene ester 19 (e.g. "Preparation of Alkenes, A Practical Approach", J.M.J. Williams, Ed., Chapter 2, "The Wittig reaction and related methods", N.J. Lawrence, Oxford University Press,

1996) to give the predominantly E-alkenyl ester 20. The E-alkenyl ester 15 is then reacted with N-trimethylsilylmethyl N-methoxymethyl benzylamine 7 under standard literature conditions (J. S. Carey, *J. Org. Chem.* 2001, 66, 2526-2529) to give the corresponding trans-substituted N-benzyl pyrrolidine-ester 21. Deprotection of the N-benzyl group (hydrogenation) gives the key intermediate, pyrrolidine-ester 22. Reaction of pyrrolidine 22 with chloroformate 10 provides pyrrolidine-carbamate ester 23. Deprotection of the ester 23 then provides the cis-substituted pyrrolidine-carbamate acids VIII of the invention.

Two alternative synthetic routes to the series of corresponding dihydropyrrole acids V of the invention are shown in Schemes 6-8. The first sequence (Schemes 6 and 7) begins with the acetylation of the hydroxy-acetylenic ester 13 to provide acetylenic acetate 24. Dipolar cycloaddition with the N-trimethylsilylmethyl N-methoxymethyl 4-methoxybenzylamine 25 (prepared as for compound 7 except using 4-methoxybenzylamine instead of benzylamine; J. S. Carey, *J. Org. Chem.* 2001, 66, 2526-2529) furnishes the corresponding dihydropyrrole-ester 26. Deoxygenation of the allylic acetate 26 (e.g. (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>-mediated; Tsuji, J., et al, *Synthesis*, 1986, 623-727) provide two isomeric alkene products: the  $\beta,\gamma$  unsaturated ester 27 and the dihydropyrrole ester 28. Deprotection of the 4-methoxybenzylamine (e.g. Yang, B. V., *Synlett*, 1993, 195-196) subsequently furnish the corresponding key amine-ester intermediates 29 and 30 respectively. Reaction of dihydropyrroles 29 and 30 with chloroformate 10 provide the pyrrolidine-carbamate esters 31 and 32 respectively. Deprotection of the esters 31 and 32 then give the dihydropyrrole-carbamate acids IX and X of the invention.

An alternative synthetic sequence (for substrates where deoxygenation of 13 occurs readily to provide 14), involves the reaction of 14 with N-trimethylsilylmethyl

N-methoxymethyl 4-methoxybenzylamine 25 (as for Scheme 6) to furnish the corresponding dihydropyrrole-ester 30 directly (shown in Scheme 8). The rest of the synthetic route to provide carbamate acids X of the invention is then identical to that shown in Scheme 5.

The synthesis of dihydropyrrole carbamate-acid analogs XI is shown in Scheme 9. Alkylation of a halogenated phenol or hydroxy-heteroarene 32 with mesylate 4 in the presence of base provides the haloarene 33. Coupling of 33 with silyl-alkyne 34 under standard Sonogashira conditions (ref. Organocopper Reagents, a Practical Approach, R. J. K. Taylor, Ed., Chapter 10, pp 217-236, Campbell, I. B., Oxford University Press, 1994) provides the arylalkyne 35. Removal of the silyl group (e.g. fluoride) followed by treatment with base and an appropriate chloroformate 36 (e.g. methyl chloroformate) furnishes the alkynoate ester 37. Dipolar cycloaddition with N-trimethylsilylmethyl N-methoxymethyl 4-methoxybenzylamine 25 furnishes the corresponding dihydropyrrole-ester 38. Deprotection of the N-methoxybenzyl amine group is achieved under standard conditions to furnish the dihydropyrrole ester 39. This intermediate then is reacted with electrophiles (e.g. chloroformate 10 in the presence of base) to provide carbamates 40. It is understood that reaction of 39 with other electrophiles (analogous to the examples in Scheme 3) can also be similarly achieved. Carbamate-esters 40 are then deprotected to furnish carbamate acids XI of the invention.

The synthesis of homologated dihydropyrrole acid XII is shown in Scheme 10. Dihydropyrrole ester 39 is suitably protected (e.g. PG, as the t-butyloxy carbamate or as the benzyloxy carbamate) as intermediate 41. Dihydropyrrole ester 41 is reduced by standard literature methods (e.g. diisobutylaluminum hydride) to give the allylic alcohol 42. Halogenation by standard literature methods (e.g. Ph<sub>3</sub>P/CBr<sub>4</sub> or PBr<sub>3</sub> to furnish the bromide;

PhP/CCl<sub>4</sub> to furnish the chloride) furnishes the corresponding allylic halide 43. Carbonylation (ref. Kiji, J. et al, *Bull. Chem. Soc. Jpn.*, 1996, 69, 1029-1031) with carbon monoxide in the presence of a ruthenium catalyst and methanol) of 43 furnishes the dihydropyrrole ester 44. Deprotection of 44 furnishes dihydropyrrole 45, which undergoes reaction with chloroformate 10 to give carbamate ester 46. Deprotection of carbamate ester 46 then furnishes dihydropyrrole acids XII of the invention.

The synthesis of cis-3,4-disubstituted pyrrolidine acids XII is shown in Scheme 11. Protected dihydropyrrole ester 41 is hydrogenated to furnish the protected cis-3,4-disubstituted pyrrolidine ester 47. Deprotection of the amine gives the pyrrolidine ester 48, which then undergoes reaction with chloroformate 10 to provide the pyrrolidine carbamate ester 49. Deprotection of esters 49 furnishes pyrrolidine carbamate-acids XIII of the invention.

The synthesis of homologated cis-3,4-disubstituted pyrrolidine acids XIV is shown in Scheme 12. Hydrogenation of intermediate dihydropyrrole ester 44 furnishes the cis-3,4-disubstituted pyrrolidine ester 50, which is then deprotected to provide pyrrolidine-ester 51. Reaction of pyrrolidine 51 with chloroformate 10 furnishes the corresponding pyrrolidine carbamate-ester 52, which is then deprotected to provide the cis-3,4-disubstituted pyrrolidine acids XIV of the invention.

An alternative synthesis of homologated pyrrolidine acids XIV is shown in Scheme 13. The pyrrolidine ester 47 is deprotected to give acid 53. Acid 53 is homologated under a standard Arndt-Eistert protocol (ref. E. Gordon et al., *J. Med. Chem.*, 1988, 31, 2199), which first involves conversion to diazoketone 54 under standard conditions (isobutyl chloroformate followed by diazomethane). Treatment of diazoketone 54 with a silver salt (e.g. silver benzoate) in the presence

of methanol provides the homologated pyrrolidine ester 50. Deprotection of pyrrolidine 50 followed by reaction with chloroformate 10 furnishes the carbamate ester 52, which is then deprotected to give homologated pyrrolidine acids XIV of the invention.

The synthesis of ether-containing analogs XV and XVI are shown in Schemes 14-15. In Scheme 14, treatment of the aldehyde 55 with the Horner-Emmons reagent 5 (W. C. Still et al., *Tetrahedron Lett.* 1985, 24, 4405-5508) provides the Z-alkenyl ester 56. This Z-alkenyl ester 56 is then reacted with N-trimethylsilylmethyl N-methoxymethyl benzylamine 7 under standard literature conditions (e.g. J. S. Carey, *J. Org. Chem.*, 2001, 66, 2526-2529) to give the corresponding N-benzyl pyrrolidine-ester 57. Reaction of halo-arene 57 with an appropriate metallating agent (e.g. isopropyl magnesium bromide, reference: P. Knochel et al., *Synthesis*, 2002, 565-569) furnishes the corresponding arylmagnesium reagent, which is then reacted with formaldehyde to provide aryl alcohol 58. Treatment of alcohol 58 with mesylate 4 in the presence of base provides the corresponding ether 59, which is then deprotected to give the pyrrolidine ester 60. Reaction of pyrrolidine 60 with chloroformate 10 provides carbamate ester 61, which is then deprotected to furnish the ether-acids XV of the invention.

In Scheme 15, treatment of the haloaryl pyrrolidine ester 57 aryl with an appropriate vinyl tin reagent (e.g. tributylvinyltin) under Stille coupling conditions (reference: Farina, V., Krishnamurthy, V., and Scott, W. J., *Organic Reactions*, 1997, 50, 1) provides the corresponding vinyl intermediate, which can then undergo hydroboration (e.g. borane-TM) to give the alcohol 62. Treatment of alcohol 62 with mesylate 4 in the presence of base provides the corresponding ether 63, which is then deprotected to furnish pyrrolidine 64. Reaction of pyrrolidine 64 with chloroformate 10 provides



carbamate ester 65, which is then deprotected to furnish the ether-pyrrolidine acids XVI of the invention.

The synthesis of carbon-linked analogs XVII is shown in Scheme 16. The halo-aryl pyrrolidine ester 57 is reacted with an appropriate heteroaryl (R')-substituted acetylene 66 in the presence of an appropriate palladium catalyst (e.g. (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>) and a copper (I) salt (e.g. CuI) in a Sonogashira coupling reaction (ref:

Organocopper Reagents, a Practical Approach, R. J. K. Taylor, Ed., Chapter 10, pp 217-236, Campbell, I. B., Oxford University Press, 1994) to furnish the arylacetylene 67. The arylacetylene ester 67 is hydrogenated to provide the corresponding pyrrolidine ester 68. Reaction of pyrrolidine 68 with chloroformate 10 provides carbamate ester 69, which is then deprotected to furnish the alkylaryl pyrrolidine acids XVII of the invention.

The synthesis of piperidine acid analogs XVIII is shown in Scheme 17. Metallation of a halo-arene 70 (e.g. isopropyl magnesium bromide, reference: P. Knochel et al., *Synthesis*, 2002, 565-569, or magnesium/anthracene, ref.) provides the corresponding organomagnesium reagent 71, which is reacted with an appropriate pyridine ester 72 in the presence of a suitable chloroformate 10 and a copper (I) salt (e.g. CuBr.SMe<sub>2</sub>) to give the corresponding dihydropyridine carbamate ester 73 (e.g. ref. D. J. Wallace et al., *Synthesis*, 2001, 1784-1789). Reduction of the dihydropyridine esters 73 (e.g. hydrogenation) furnishes piperidine carbamate ester 74, which is then deprotected to give the phenol 75. Reaction of phenol 75 with mesylate 4 in the presence of base provides the piperidine carbamate ester 76, which is then deprotected to furnish pyrrolidine carbamate acids XVIII of the invention.

The synthesis of tetrahydropyridine acids XIX is shown in Scheme 18. An appropriately protected piperidone 77 is reacted with aldehyde 78 in the presence

of base (standard aldol reaction) followed by deoxygenation to furnish the 2-alkyl piperidone 79.

Treatment of 79 with triflic anhydride in the presence of base (e.g. iPr<sub>2</sub>NMg) under thermodynamic conditions furnishes enol triflate 80. Palladium-mediated carbonylation under standard literature conditions (e.g. S. K. Thompson et al., *J. Org. Chem.*, 1990, 55, 3004) with carbon monoxide in the presence of an alcohol (preferably methanol) furnishes the tetrahydropyridine ester 81. Deprotection of 81 provides phenol 82, which is alkylated with mesylate 4 to give the tetrahydropyridine ester 83. Deprotection of 83, followed by reaction with chloroformate 10, furnishes tetrahydropyridine carbamate ester 84. Deprotection of carbamate ester 84 give tetrahydropyridine carbamate-acids XIX of the invention.

The synthesis of cis 3,4-disubstituted piperidine acids XX is shown in Scheme 19. Tetrahydropyridine ester 83 is reduced (hydrogenation) to give the cis 3,4-disubstituted piperidine ester 85. Deprotection of the piperidine 85, followed by reaction with chloroformate 10, provides piperidine carbamate ester 86. Deprotection of carbamate ester 86 provides cis 3,4-disubstituted piperidine carbamate-acids XX of the invention.

The synthesis of piperazine acids XXI (where in Formula I q = 1, Z is a bond, p = 2 and E is nitrogen) is shown in Schemes 20A and 20B. In Scheme 20A reductive amination of aldehyde 78 with a readily available monoprotected piperazine ester 87 furnishes the alkylated piperazine ester 88. Deprotection of 88 provides the phenol 89, which is alkylated with mesylate 4 in the presence of base to furnish the alkylated piperazine ester 90. Selective deprotection of the amine followed by reaction with chloroformates 10 provides piperazine carbamate-esters 91. Deprotection of carbamate-esters 91 furnishes piperazine carbamate-acids XXI of the invention.

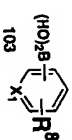
Alternatively, piperazine carbamate-acids XXI can also be synthesized according to the synthetic sequences shown in Scheme 20B. Reductive amination of the monoprotected piperazine ester 87 with aldehyde 3 directly provides the key intermediate alkylated piperazine ester 90. As described for Scheme 20A, a 3-step sequence involving: 1) selective deprotection of the amine functionality of 90; 2) reaction with chloroformates 10 and 3) deprotection of the acid, furnishes piperazine carbamate-acids XXI of the invention. In addition, complete deprotection of piperazine-ester 90 provides piperazine acid 92, which is then reacted with chloroformates 10 to furnish piperazine carbamate-acids XXI of the invention.

The synthesis of azetidone-acids XXII (in Formula I where Z is a bond, q = 0, p = 1 and E = CH) is shown in Scheme 21. The hydroxyaryl ester 93 is alkylated with mesylate 4 under basic conditions, then deprotected to provide the acid 94. Acid 94 is converted to the corresponding acid chloride under standard conditions (oxalyl chloride in the presence of a catalytic amount of dimethyl formamide), then is treated with a bis-imine such as 95 under Staudinger conditions (reference: R. M. Adlington et. al., *J. Med. Chem.*, 2001, 44, 1491) to furnish the key intermediate  $\beta$ -lactam aldehyde 96. Protection of the aldehyde 96 (e.g. as the dimethyl acetal) followed by reduction of the resulting  $\beta$ -lactam acetal (e.g.  $\text{AlH}_3\text{Cl}$ , reference: B. Alcalde et. al. *J. Org. Chem.*, 1999, 64, 9596) furnishes the corresponding azetidone acetal 97. Deprotection of the azetidone under standard conditions (e.g. ceric ammonium nitrate) followed by reaction with chloroformates 10 furnishes the corresponding azetidone-carbamates. Deprotection of the aldehyde under standard conditions (aqueous acid) followed by a standard oxidation of the aldehyde (e.g.  $\text{NaClO}_2/\text{H}_2\text{SO}_4\text{H}$ ; reference: B. O. Lindgren et. al., *Acta Chem. Scand.*, 1973, 27, 888 or E. Dalcanaile et. al., *J.*

*Org. Chem.*, 1986, 51, 567) provides the azetidone carbamate-acids XXII of the invention.

Direct oxidation of the intermediate  $\beta$ -lactam aldehyde 96 (e.g. the Lindgren oxidation) furnishes the azetidone acids XXIII of the invention.

A general method for synthesis of the cis-disubstituted  $\beta$ -lactam acids XXIV and the corresponding trans-disubstituted azetidone-acids XXV is depicted in Scheme 22. A suitably protected carboxylic acid 98 (e.g.,  $\text{PG}_1$  = benzyl) is converted to the acid chloride 99, which upon treatment with a suitably substituted bis-imine (e.g. 95) undergoes a Staudinger reaction (reference: R. M. Adlington et. al., *J. Med. Chem.*, 2001, 44, 1491) to furnish the key intermediate  $\beta$ -lactam aldehyde 100. Oxidation of aldehyde 100 to the corresponding carboxylic acid (e.g. Lindgren oxidation) followed by protection (esterification) provides the  $\beta$ -lactam ester 101. Removal of the N-4-methoxyphenyl group provides the corresponding deprotected  $\beta$ -lactam ester 102, which then is reacted with a variety of diverse aryl boronic acids 103



103  $\text{X}_1$ , where  $\text{R}^8$  is H, alkyl, alkoxy, halogen, amino or substituted amino, and  $\text{X}_1$  is CH or N) under copper-mediated catalysis (Chan, D. M. T. et al. *Tetrahedron Lett.* 1998, 39, 2933; Evans, D. A. et al. *Tetrahedron Lett.* 1998, 39, 2937) to provide the corresponding N-aryl esters 104. Deprotection of the phenol followed by alkylation of the phenol with mesylate 4 under basic conditions provides the alkylated  $\beta$ -lactam ester 105. Appropriate deprotection of the  $\beta$ -lactam ester 105 gives a mixture of the cis-disubstituted trans-azetidone acids XXIV and the epimerized trans-disubstituted azetidone acids XXV of the invention. An alternative synthesis of azetidone acids XXIII is illustrated in Scheme 23. Deprotection of the phenol

moiety of azetidinone-ester 101 provides the phenol 102, which undergoes base-mediated alkylation using mesylate 4 to give the alkylated phenol azetidinone-ester 107.

Removal of the final protecting group provides the azetidinone acids XXIII. Yet another route to acids XXIII is shown in Scheme 24). The  $\beta$ -lactam aldehyde intermediate 100 is reduced by standard methods (e.g.  $\text{NaBH}_4$ ), after which the phenol is deprotected to give the phenol-azetidinone alcohol 108. Alkylation of 108 with mesylate 4 provides the alkylated phenol azetidinone alcohol 109, which is then oxidized under standard literature conditions (e.g. Jones reagent) to give the azetidinone acids XXIII of the invention.

It should be noted that in Schemes 21-24, a number of the racemic intermediates (e.g. 102 and 107) as well as the final product azetidinone-acids XXIII-XXV, are amenable to separation into their individual enantiomers by chiral preparative HPLC.

An approach to the direct asymmetric synthesis of the key chiral azetidinone intermediate 112 is shown in Scheme 25. A chiral ligand-mediated coupling of the acid chloride 99 with suitably protected carboxy-tosyl imines such as 110 (Ref: Taggi, A. E. et al. *J. Am. Chem. Soc.* 2002, 124, 6626) affords the chiral cis-disubstituted  $\beta$ -lactam 111 with high enantioselectivity. N-deprotection of the tosylated  $\beta$ -lactam 111 furnishes the corresponding  $\beta$ -lactam, which then is reacted with diverse aryl boronic acids 103 under copper-mediated catalysis (Chan, D. M. T. et al. *Tetrahedron Lett.* 1998, 39, 2933; Evans, D. A. et al. *Tetrahedron Lett.* 1998, 39, 2937) to provide the corresponding N-aryl esters 112. The chiral intermediate 112 can be processed as before to furnish chiral azetidinone-acids XXIII-XXV of the invention as described in Schemes 21-24 and 26.

An alternative approach to N-carbamate azetidine acids XXII is shown in Scheme 26. Reduction of the azetidinone-aldehyde intermediate 100 (e.g. with

chloroalane) provides the N-aryl azetidine alcohol 113. Deprotection of the N-aryl azetidine to the corresponding azetidine followed by reaction with appropriate chloroformates 10 affords the N-carbamate azetidine alcohols 114. Oxidation of azetidine alcohol 114 to the acid (e.g. Jones reagent) followed by protection of the acid (esterification) provides the azetidine carbamate ester 115. Deprotection of 115 gives the free phenol 116, which undergoes base-mediated reaction with mesylate 4 to give the alkylated azetidine carbamate ester 117. Finally, deprotection of 117 provides the desired carbamate acids XXII of the invention.

The synthesis of the corresponding N-Aryl azetidine acids XXVI is shown in Scheme 27. Reduction of either racemic N-aryl azetidinone ester 104 or chiral N-aryl azetidinone ester 112 (e.g. chloroalane) provides the corresponding azetidine-alcohol 118. Deprotection of the phenol of 118 followed by alkylation with mesylate 4 and finally oxidation (e.g. Jones reagent) provides the N-aryl azetidine acids XXVI of the invention.

The azetidinone acids XXVII and the pyrrolidinone acids XXVIII may be obtained following the general procedure shown in Scheme 28 (literature precedent: Wee, A. G. H.; Liu, B.-S.; Zhang, L. *J. Org. Chem.*, 1992, 57(16), 4404; also Wee, A. G. H.; Liu, B. *Tetrahedron Lett.* 1996, 37(2), 145-148). The intermediate aniline 121 can be synthesized either by: a) reductive amination (e.g. with  $\text{NaBH}(\text{OAc})$ ) of aldehyde 3 with an appropriate aniline or b) an aniline carbamate 119 can be alkylated with an alkyl halide 120 in the presence of a base (e.g.  $\text{NaH}$ ) and then the carbamate can be removed with a nucleophilic base (e.g.  $\text{KOH}$ ). Acylation of aniline 121 with the malonyl acid chloride 122 in the presence of base (e.g.  $\text{Et}_3\text{N}$  or pyridine or DMAP) provides the malonyl amide 123. Treatment of the  $\beta$ -ketoamide 123 with an appropriate diazotization agent (e.g. methanesulfonyl azide) in the presence of base (e.g. DBU) provides the

azetidinone acids XXVII and the pyrrolidinone acids XXVIII may be obtained following the general procedure shown in Scheme 28 (literature precedent: Wee, A. G. H.; Liu, B.-S.; Zhang, L. *J. Org. Chem.*, 1992, 57(16), 4404; also Wee, A. G. H.; Liu, B. *Tetrahedron Lett.* 1996, 37(2), 145-148). The intermediate aniline 121 can be synthesized either by: a) reductive amination (e.g. with  $\text{NaBH}(\text{OAc})$ ) of aldehyde 3 with an appropriate aniline or b) an aniline carbamate 119 can be alkylated with an alkyl halide 120 in the presence of a base (e.g.  $\text{NaH}$ ) and then the carbamate can be removed with a nucleophilic base (e.g.  $\text{KOH}$ ). Acylation of aniline 121 with the malonyl acid chloride 122 in the presence of base (e.g.  $\text{Et}_3\text{N}$  or pyridine or DMAP) provides the malonyl amide 123. Treatment of the  $\beta$ -ketoamide 123 with an appropriate diazotization agent (e.g. methanesulfonyl azide) in the presence of base (e.g. DBU) provides the

5 diazoester 124. Rhodium-mediated intramolecular  
cyclization (by C-H insertion) of diazo-ester 124  
provides a mixture of the corresponding azetidione and  
pyrrolidinone esters. Deprotection of these esters  
provides the azetidione acids XXVII of the invention as  
a mixture of diastereomers (cis and trans) and the  
pyrrolidinone acids XXVIII as a mixture of diastereomers  
(cis and trans) of the invention. The ratio of products  
XXVII and XXVIII can be controlled by an appropriate  
choice of the substituent on the aniline moiety.

10 An alternative synthesis of piperidine carbamate-  
acids XIX and piperidine N-aryl acids XXIX is shown in  
Scheme 29. Treatment of an appropriately protected aryl  
substituted halide 70 with activated zinc provides the  
aryl zinc reagent 125 (ref: Rieke, R., et al., *J. Org.*  
15 *Chem.*, 1991, 56, 1445-1453). An appropriately protected  
piperidone ester 126 is converted to the corresponding  
enol nonafiate 127 under standard literature conditions  
(ref: Bellina, F. et al, *Tetrahedron*, 1999, 55, 2103-  
2112). Treatment of enol nonafiate 127 with the aryl  
20 zinc reagent 125 in the presence of a palladium catalyst  
(ref: Bellina, F. et al, *Tetrahedron*, 1999, 55, 2103-  
2112) provides the coupled  $\alpha,\beta$ -unsaturated ester 81. The  
phenol of 81 is deprotected and alkylated with mesylate 4  
(as for Scheme 18) to provide the piperidine ester 83.  
25 Hydrogenation and N-deprotection of 83 furnishes the key  
piperidine ester 128, which is then converted according  
to the sequence in Scheme 19 to the piperidine carbamate  
acids XX of the invention.

30 As shown in Scheme 30, the intermediate piperidine  
ester 128 can also be reacted with aryl or heteroaryl  
halides in the presence of a palladium catalyst (e.g.  
method of Buchwald et. al., *J. Am. Chem. Soc.*, 2001, 123,  
7727) to furnish the N-aryl or N-heteroaryl piperidine  
35 acids XXIX of the invention. Alternatively, intermediate  
piperidine ester 128 can also be reacted directly with  
electron-deficient heteroaryl halides in the presence of

base to give N-heteroaryl piperidine acids XXX of the  
invention.

5 Scheme 31 shows the synthesis of the  $\alpha,\beta$ -  
unsaturated piperidine acids. The phenol moiety of the  
N-protected piperidine ester 81 is deprotected and  
alkylated with mesylate 4 to provide alkylated phenol 83,  
which is then deprotected to furnish the key free  
piperidine intermediate 129. Intermediate 129 is treated  
with an appropriate chloroformate 10 and deprotected to  
10 give piperidine carbamate-acids XIX of the invention (as  
for Scheme 18). Alternatively, piperidine 129 can be  
treated with an aryl halide or a heteroaryl halide in the  
presence of a palladium catalyst (e.g. method of Buchwald  
et. al., *J. Am. Chem. Soc.*, 2001, 123, 7727) followed by  
15 deprotection of the acid to furnish the N-aryl or N-  
heteroaryl piperidine acids XXXI and XXXII of the  
invention. In addition, electron-deficient heteroaryl  
halides can be directly reacted with piperidine  
intermediate 129 in the presence of base followed by  
20 deprotection of the acid to provide N-heteroaryl  
piperidine acids XXXII of the invention.

The synthesis of  $\beta,\gamma$ -unsaturated piperidine acids  
XXXIII-XXXV of the invention is shown in Scheme 32. The  
piperidine  $\alpha,\beta$ -unsaturated ester intermediate 129 is  
25 reacted with a chloroformate 10 to provide the  
corresponding piperidine carbamate  $\alpha,\beta$ -unsaturated ester  
130. Base-mediated deprotection of the acid (ester  
hydrolysis) furnished the piperidine carbamate  $\beta,\gamma$ -  
unsaturated acids XXXIII of the invention. Similarly,  
30 reaction of piperidine 129 with aryl halides in the  
presence of a palladium catalyst (as for Scheme 31)  
provided the corresponding N-aryl piperidine  $\alpha,\beta$ -  
unsaturated ester, which upon base hydrolysis furnished  
the N-aryl piperidine  $\beta,\gamma$ -unsaturated acids XXXIV of the  
35 invention. Reaction of piperidine 129 with  $\pi$ -deficient  
heteroaryl halides in the presence of base provided the  
corresponding N-heteroaryl piperidine  $\alpha,\beta$ -unsaturated

ester, which upon base hydrolysis furnished the N-heteroaryl piperidine  $\beta,\gamma$ -unsaturated acids XXXV of the invention.

The preparation of pyrrolidinone acids XXXVI of the invention is shown in Scheme 33. A suitably protected pyrrolidinone ester 130 is deprotonated with an appropriate base (e.g. lithium diisopropylamide) and alkylated with a protected aryl halide 70 to furnish the alkylated pyrrolidinone ester 131. The phenol of pyrrolidinone ester 131 is deprotected and alkylated with mesylate 4 to provide pyrrolidinone ester 132, which is N-deprotected to give the key pyrrolidinone ester intermediate 133. Palladium-mediated arylation with an appropriate arylboronic acid followed by deprotection of the acid provides pyrrolidinone acids XXXVI of the invention.

The preparation of pyrrolidinone acids XXXVII and XXXIX of the invention is shown in Scheme 34. The appropriately protected pyrrolidinone ester 134 is deprotonated with an appropriate base (e.g. lithium diisopropylamide) and alkylated with halide 70 to provide the alkylated lactam ester 135 (ref: Saksena, A. K., et al., Patent PCT W00208256; August, R. A., *J. Chem. Soc. Perkin 1*, 1996, 507-514). Deprotection of the phenol moiety of 135 followed by alkylation with mesylate 4 in the presence of base gives the alkylated phenol lactam ester 136. N-Deprotection of the lactam provides the key intermediate lactam 137, which is reacted with appropriate aryl boronic acids to provide the corresponding N-aryl lactam ester followed by deprotection of the acid to provide N-aryl pyrrolidinone acids XXXVII of the invention. Alternatively, after lactam 137 is reacted with aryl boronic acids to provide the corresponding N-aryl lactam ester, the lactam is reduced (e.g. 2 step sequence: a) LiBHET<sub>3</sub>, b) Et<sub>3</sub>SiH/BF<sub>3</sub>·OEt<sub>2</sub>; ref: Ezquerro, J., *J. Org. Chem.*, 1995, 60, 2925-2930) to the corresponding pyrrolidinone ester,

which is then deprotected to give the N-aryl pyrrolidine acids XXXIX of the invention.

The preparation of N-substituted pyrrolidine acids XXXVIII-XXXX of the invention is shown in Scheme 35. The lactam ester 136 is reduced (e.g. 2 step sequence: a) LiBHET<sub>3</sub>, b) Et<sub>3</sub>SiH/BF<sub>3</sub>·OEt<sub>2</sub>) to the corresponding pyrrolidine ester, which then undergoes N-deprotection to provide the key intermediate pyrrolidine ester 139. Reaction of pyrrolidine 139 with chloroformates 10 provide the carbamate pyrrolidine ester 140, which is then deprotected to furnish carbamate pyrrolidine acids XXXVIII of the invention. Reaction of pyrrolidine 139 with aryl halides in the presence of a palladium catalyst (as for Scheme 31) provided the corresponding N-aryl pyrrolidine ester, which upon deprotection of the acid furnished the N-aryl pyrrolidine acids XXXIX of the invention. Reaction of pyrrolidine 139 with  $\pi$ -deficient heteroaryl halides in the presence of base or under palladium catalysis provided the corresponding N-heteroaryl pyrrolidine ester, which upon deprotection of the acid furnished the N-heteroaryl pyrrolidine acids XXXX of the invention.

The synthesis of pyrrolidine acids XLI-XLIII of the invention is shown in Scheme 36. The benzamide-protected  $\alpha$ -amino ester 141 is alkylated with mesylate 4 in the presence of base to furnish the alkylated phenol 142. Reduction of the benzamide and ester (e.g. LiAlH<sub>4</sub> or LiBH<sub>4</sub>) followed by Michael reaction of the resultant amine with acrylonitrile in the presence of base to give the  $\beta$ -amino-nitrile 143. Chlorination of the alcohol 143 (e.g. with SOCl<sub>2</sub>) followed by base (e.g. NaN(TMS)) mediated intramolecular cyclization provides the cyano-pyrrolidine 144. This sequence is preceded in the literature (R. Achini, *Helv. Chim. Acta*, 1981, 64, 2203-2218). Acid-mediated hydrolysis (e.g. H<sub>2</sub>SO<sub>4</sub>) of the nitrile in the presence of an appropriate alcohol provides the corresponding pyrrolidine ester, which is debenzylated

(e.g. hydrogenation) to provide the key pyrrolidine ester intermediate 145. Reaction of pyrrolidine 145 with chloroformates 10 provide the corresponding carbamate pyrrolidine ester, which is then deprotected to furnish

5 carbamate pyrrolidine acids XLI of the invention.

Reaction of pyrrolidine 145 with aryl halides in the presence of a palladium catalyst (as for Scheme 31) provided the corresponding N-aryl pyrrolidine ester, which upon deprotection of the acid furnished the N-aryl pyrrolidine acids XLII of the invention. Reaction of pyrrolidine 145 with  $\pi$ -deficient heteroaryl halides in the presence of base or under palladium catalysis provided the corresponding N-heteroaryl pyrrolidine ester, which upon deprotection of the acid furnished the N-heteroaryl pyrrolidine acids XLIII of the invention.

15 An asymmetric synthesis of pyrrolidine acids XLIV and XLV is shown in Scheme 37. The maleimide 146 is

reacted with N-trimethylsilylmethyl N-methoxymethyl benzylamine 7 under standard literature conditions (e.g. J. S. Carey, *J. Org. Chem.*, 2001, 66, 2526-2529) to give the corresponding N-benzyl pyrrolidine-ester 147. The imide 147 is then reacted with an appropriately protected aryl Grignard reagent 148; the intermediate hydroxy lactam is reduced (e.g. NaBH<sub>4</sub>) and thermally-induced intramolecular cyclization provides the lactone 149.

25 Deprotection of the phenol moiety of lactone 149 followed by base-mediated alkylation of the phenol with mesylate 4 provides the alkoxyphenol lactone 150. Deprotection (hydrogenation) of the N-benzyl group with concomitant

30 hydrogenolysis of the benzylic lactone C-O bond provides the pyrrolidine acid 151, which is reprotected with an appropriate alcohol to furnish the key intermediate pyrrolidine ester 152. Reaction of 152 with an

appropriate chloroformate 10 and acid deprotection (as for Scheme 4) provides chiral pyrrolidine carbamate acids XLIV of the invention. Reaction of 152 with appropriate aryl halides or heteroaryl halides followed by acid

deprotection (as for Scheme 35) provides chiral N-aryl pyrrolidine acids XLV and chiral N-heteroaryl pyrrolidine acids XLVI of the invention respectively.

5 The synthesis of hydantoin acids XLVII of the invention is shown in Scheme 38. Reductive amination (e.g. NaBH(OAc)<sub>3</sub> or NaBH<sub>3</sub>CN) of aryl aldehyde 3 with an aspartate derivative 153 gives the amino-diester 154. Reaction of amino-diester 154 with appropriate aryl isocyanates 155 with heat results in the formation of hydantoin ester 156. Deprotection of hydantoin ester 156 provides hydantoin acids XLVII of the invention. It should be noted that the use of L- or S-aspartate diesters provides the individual enantiomers of hydantoin acids XLVII of the invention.

15 The synthesis of piperidine acids XLVIII-L of the invention is shown in Scheme 39. Reaction of the  $\alpha$ -carboalkoxy piperidone 157 with nonafllyl fluoride in the presence of base provides the enol nonaflate 158.

20 Palladium mediated coupling of enol nonaflate 158 with the organozinc reagent 125 (as previously described for Scheme 29; ref: (Bellina, F. et al, *Tetrahedron*, 1999, 55, 2103-2112)) provides the coupled  $\alpha,\beta$ -unsaturated ester 159. The phenol of 159 is deprotected and

25 alkylated with mesylate 4 (as for Scheme 18) to provide the piperidine ester 160. N-deprotection of 160 furnishes the key piperidine ester 161, which is then

converted according to the sequence in Scheme 37 to the piperidine carbamate acids XLVIII of the invention, the N-aryl piperidine acids XLIX of the invention and N-heteroaryl piperidine acids L of the invention.

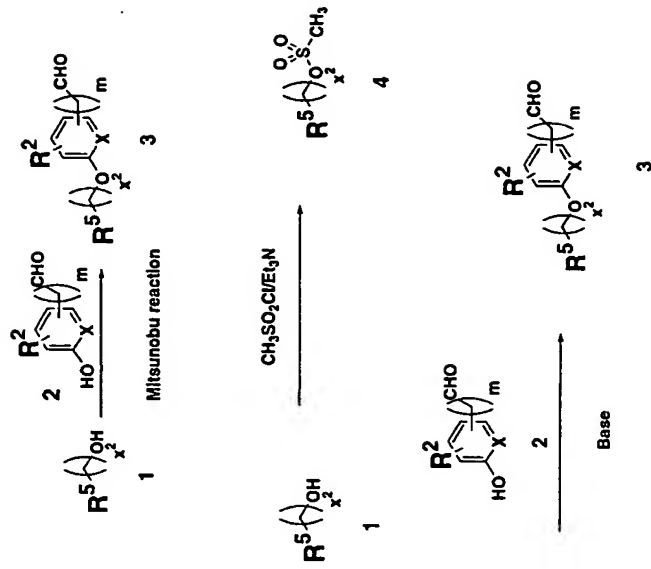
30 The preparation of piperidine acids LI-LIII of the invention is shown in Scheme 40. Treatment of  $\alpha$ -carboalkoxy piperidone 157 with triflic anhydride in the presence of base provides enol triflate 162. Palladium-mediated coupling of enol triflate 162 to an appropriately substituted aryl boronic acid 163 (ref: Wustrow, D.J. and Wise, L.D., *Synthesis*, 1991, 993-995)

provides the coupled piperidine  $\alpha, \beta$  unsaturated ester 164. Deprotection of the phenol moiety of 164 followed by alkylation with mesylate 4 provides the alkoxy phenol piperidine ester 165, which is then N-deprotected to furnish the free piperidine ester 166.

Piperidine ester 166 is then converted according to the sequences shown in Scheme 37 to the piperidine carboxylic acids LI of the invention, the N-aryl piperidine acids LII of the invention and N-heteroaryl piperidine acids LIII of the invention.

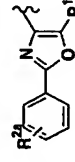
Scheme 41 illustrates the synthesis of piperidine acids LIV-LVI of the invention. Reduction (hydrogenation) of the  $\alpha, \beta$  unsaturated ester 166 provides the corresponding piperidine ester 167. Piperidine ester 167 is then converted according to the sequences shown in Scheme 37 to the piperidine carboxylic acids LIV of the invention, the N-aryl piperidine acids LV of the invention and N-heteroaryl piperidine acids LVI of the invention.

20

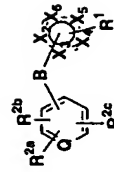


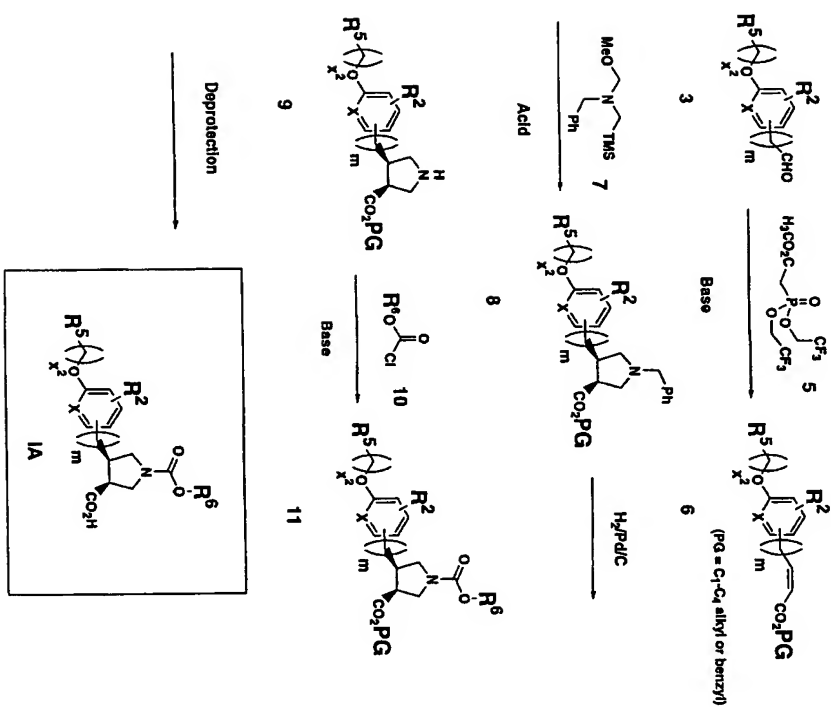
Scheme 1

In this and the following Reaction Schemes,  $R^5 =$

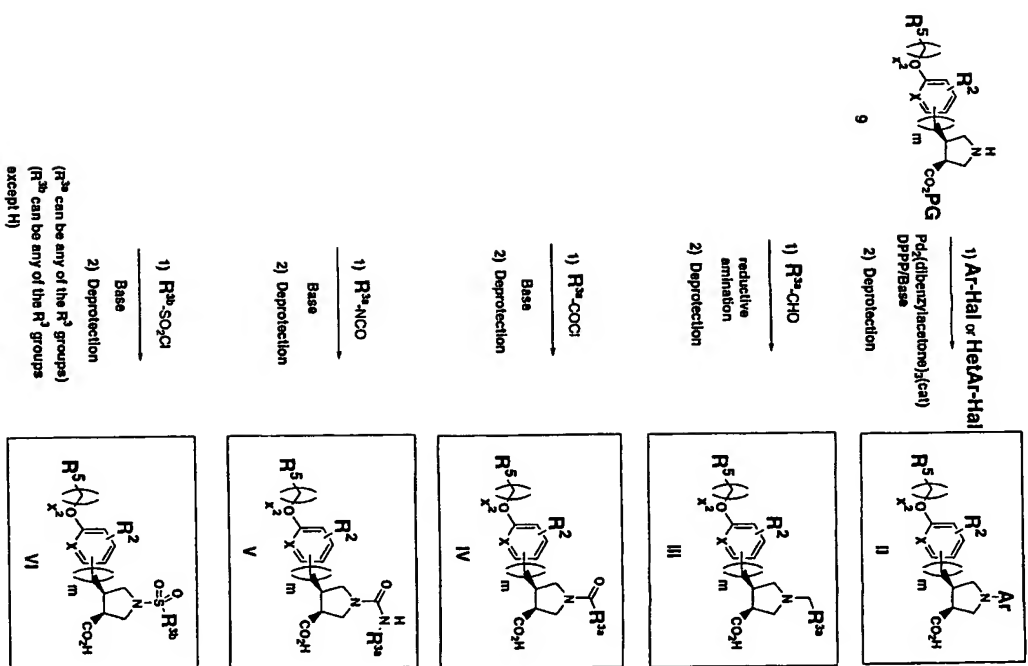


preferably  $R^5 =$



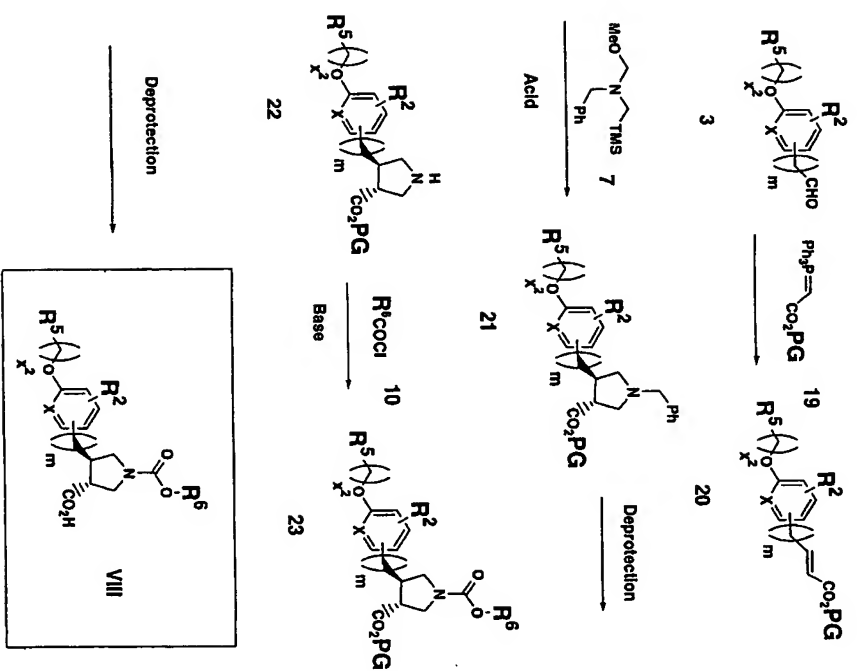


SCHEME 2

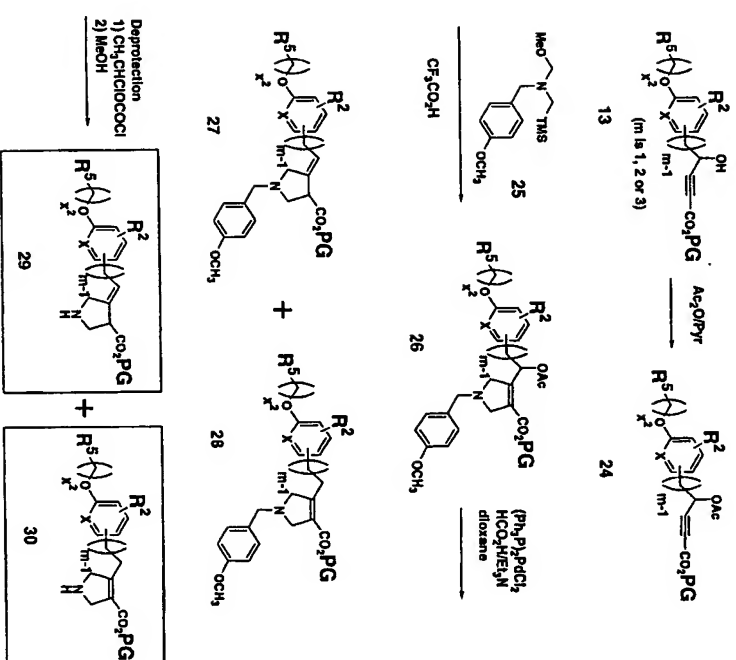




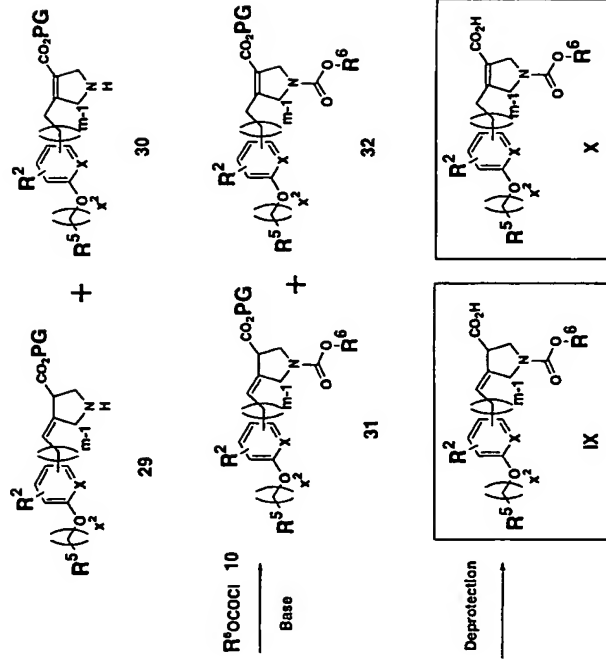




Scheme 5

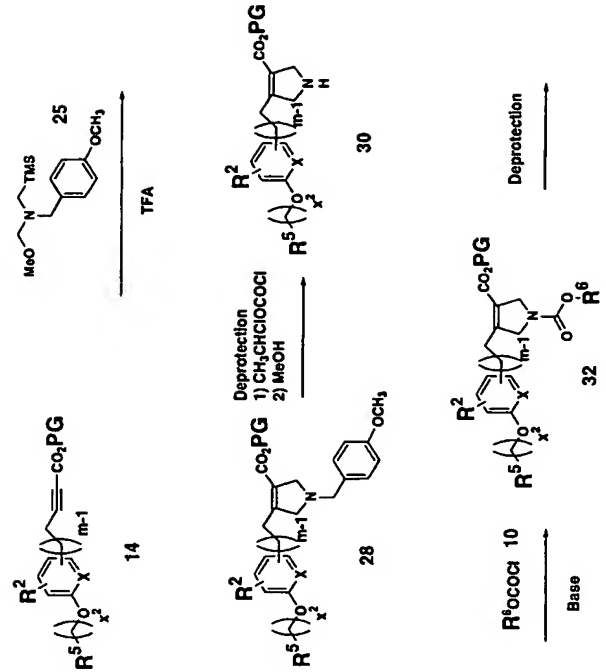


Scheme 6

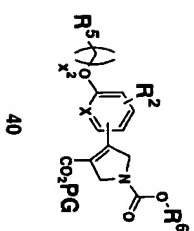
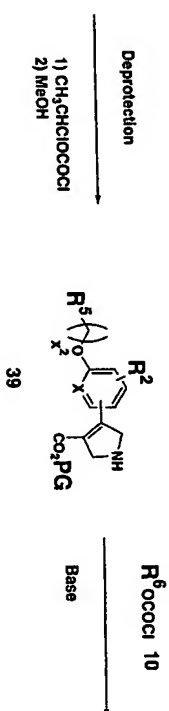
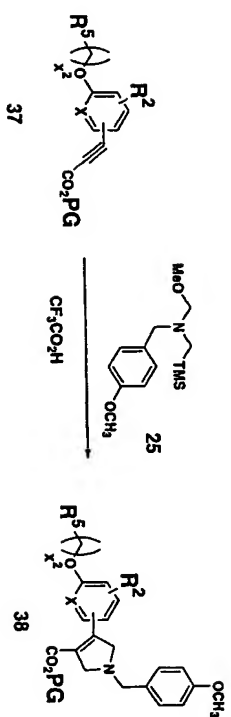
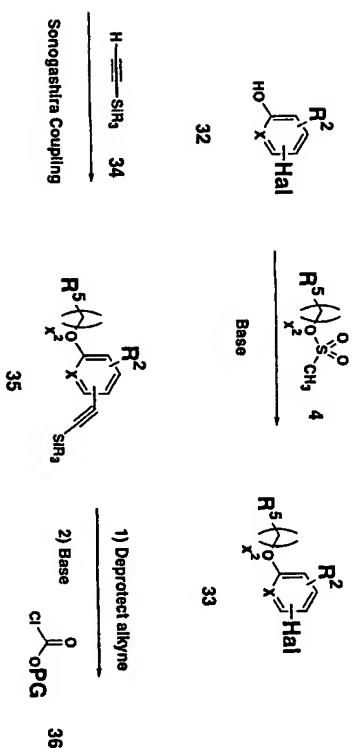


Scheme 7

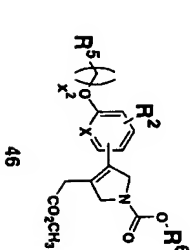
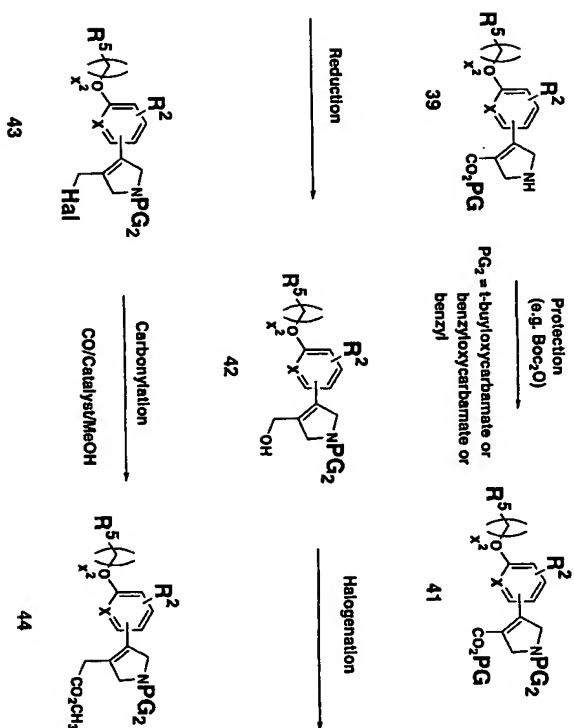
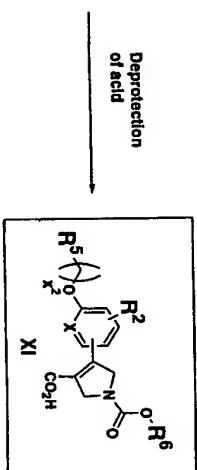
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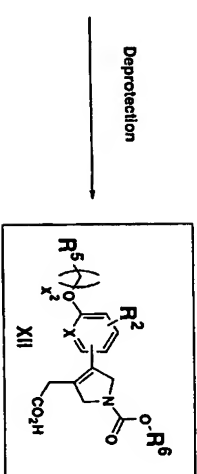
Scheme 8

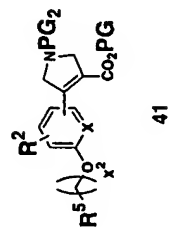


Scheme 9

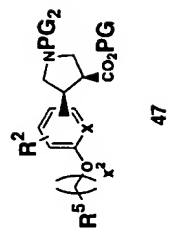


Scheme 10

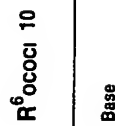
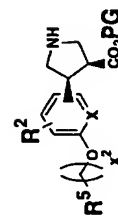




Hydrogenation

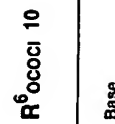
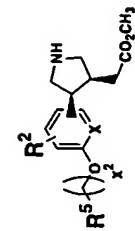


Deprotection of amine

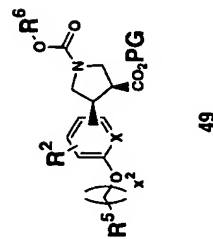


Base

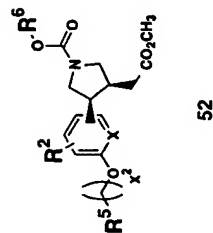
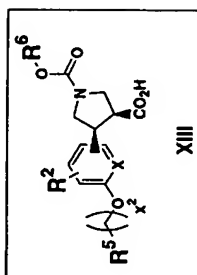
Deprotection of amine



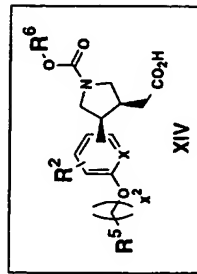
Base



Deprotection of acid

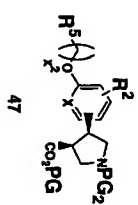


Deprotection of acid

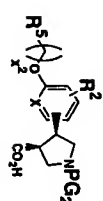


Scheme 11

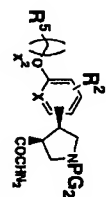
Scheme 12



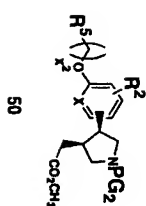
Deprotection of  
Acid



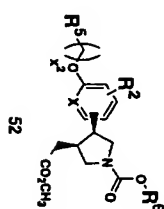
1) BuOCOCbase  
2) CH<sub>2</sub>N<sub>2</sub>  
Arndt-Eistert  
Homologation



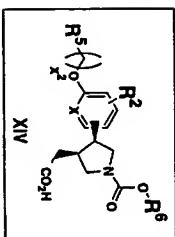
Silver salt  
MeOH



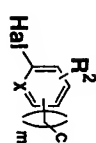
1) Deprotect amine  
2) Base



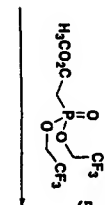
Deprotection  
of acid



Scheme 13

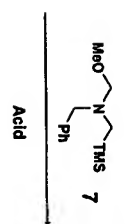
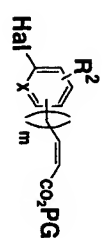


Base

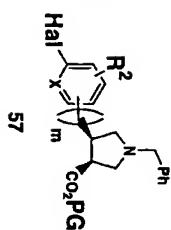


Base

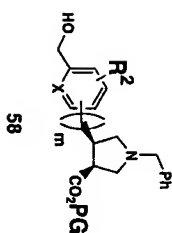
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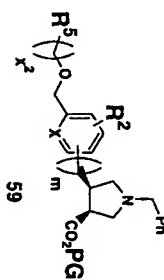
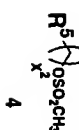
Acid



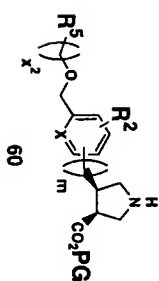
1-PrMgBr  
-20°C  
formaldehyde



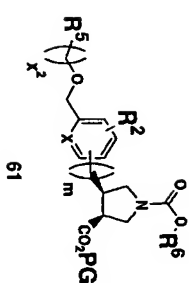
Base



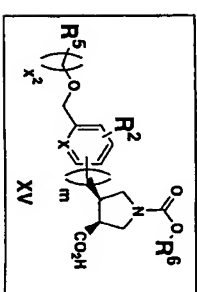
Deprotection  
(Hydrogenation)



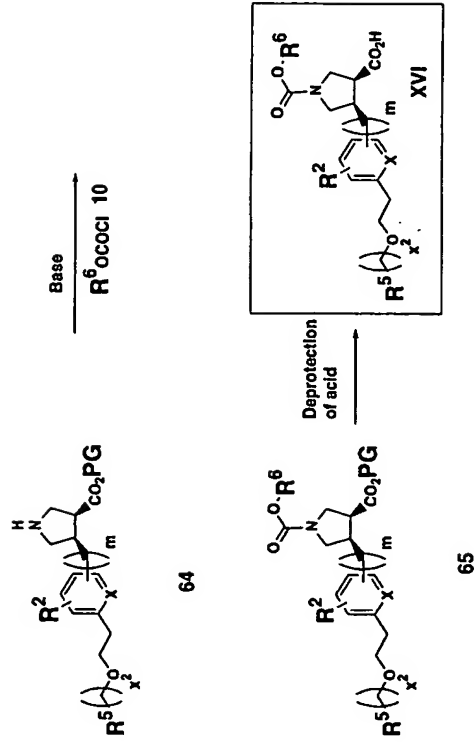
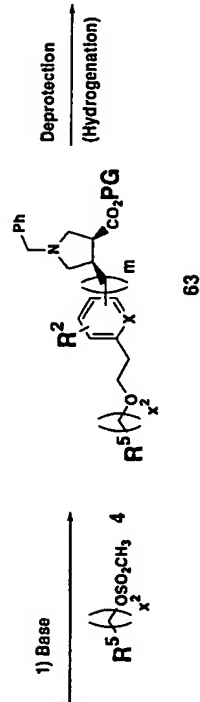
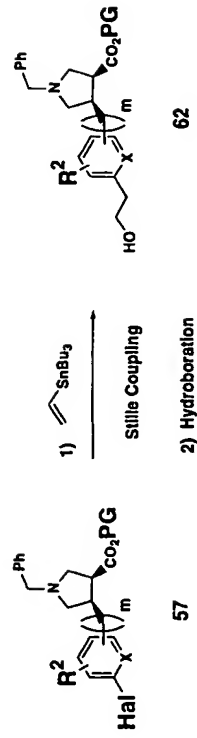
Base  
R<sup>6</sup>OCCl 10



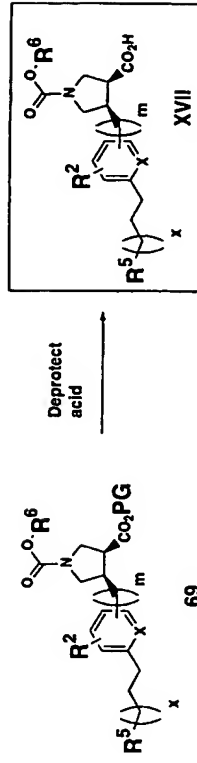
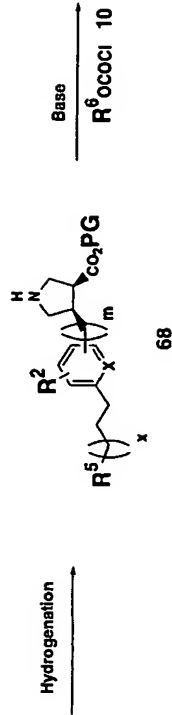
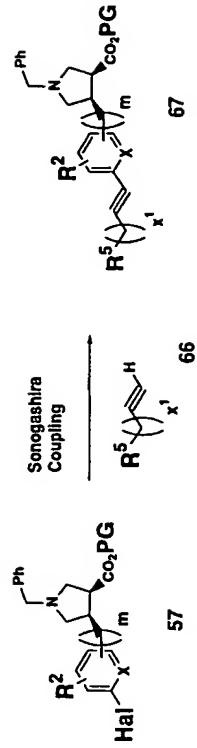
Deprotect  
acid



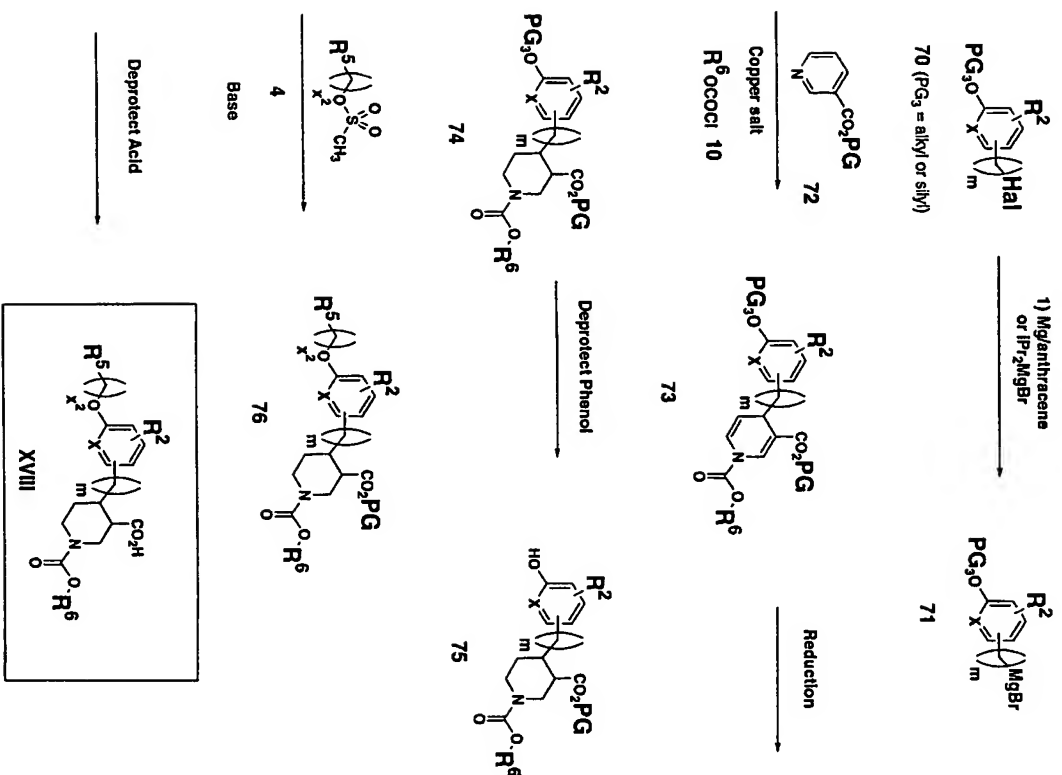
Scheme 14



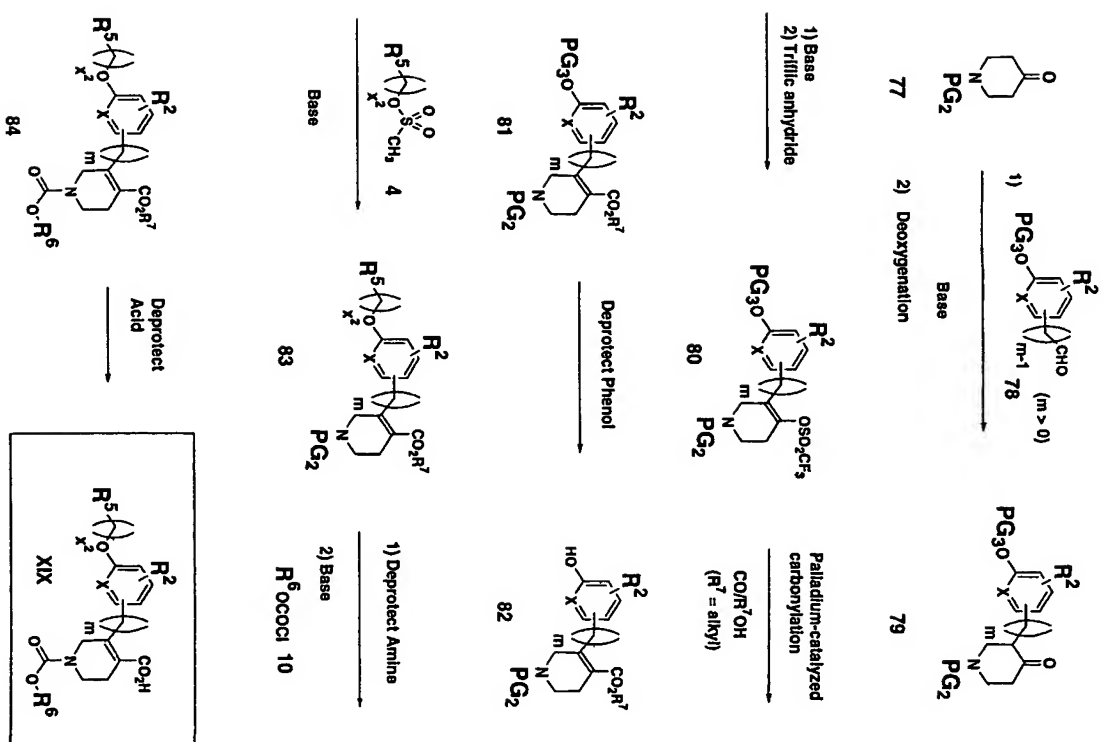
SCHEME 15



SCHEME 16

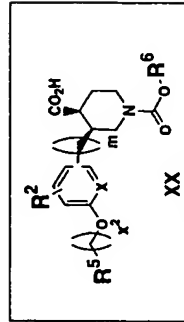
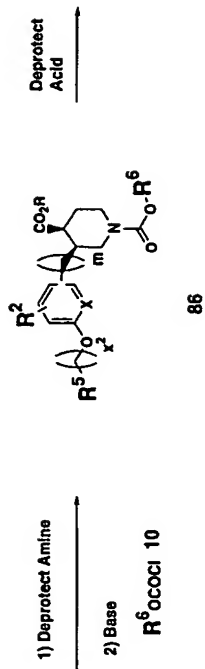
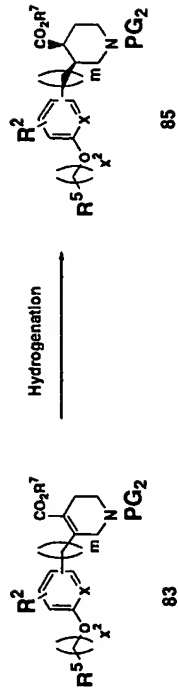


**SCHEME 17**

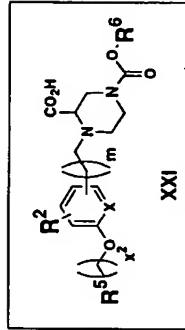
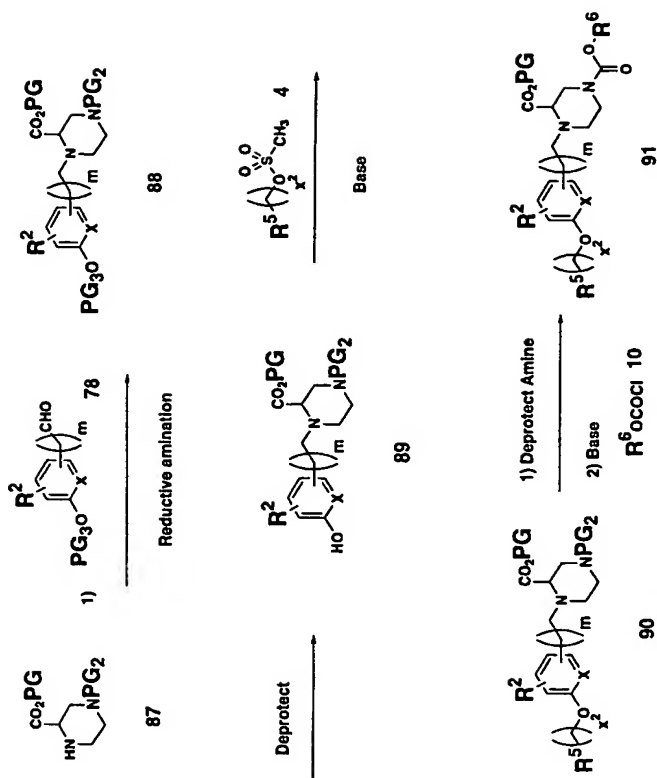


**SCHEME 18**

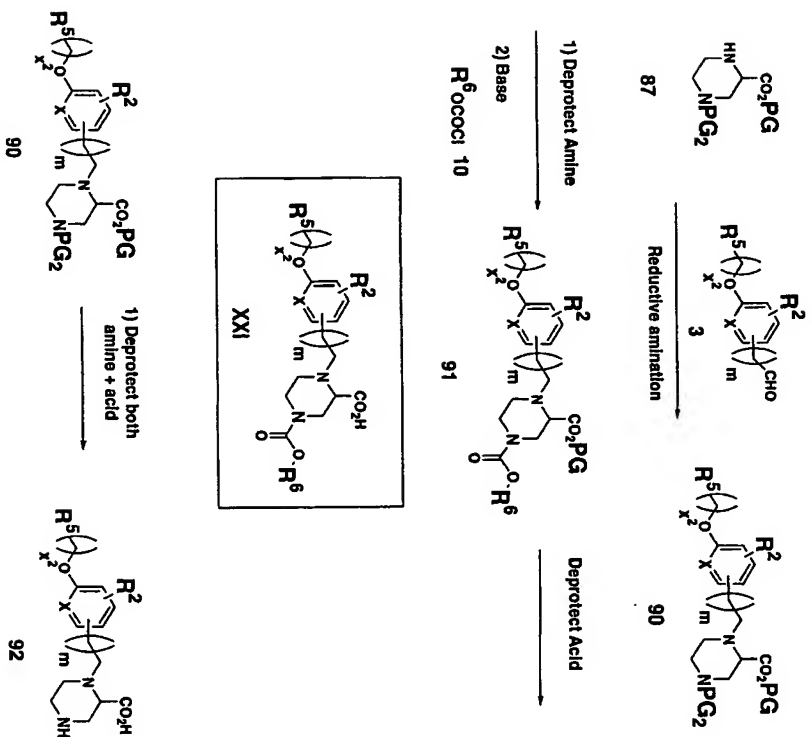




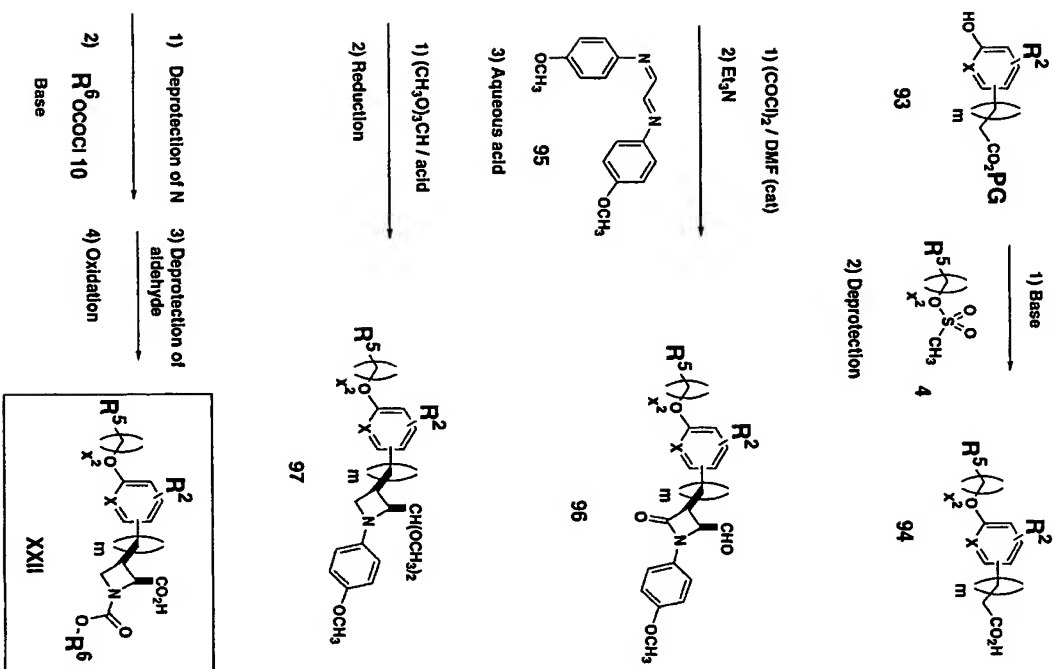
SCHEME 19



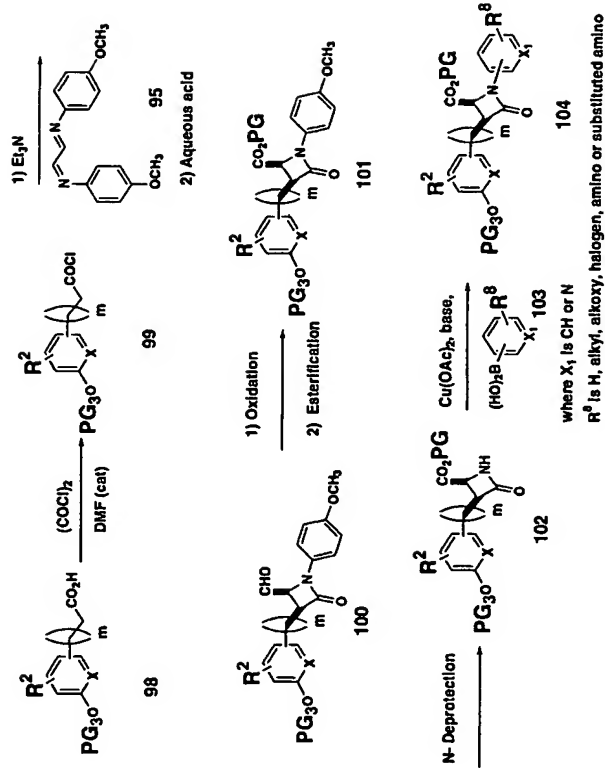
SCHEME 20A



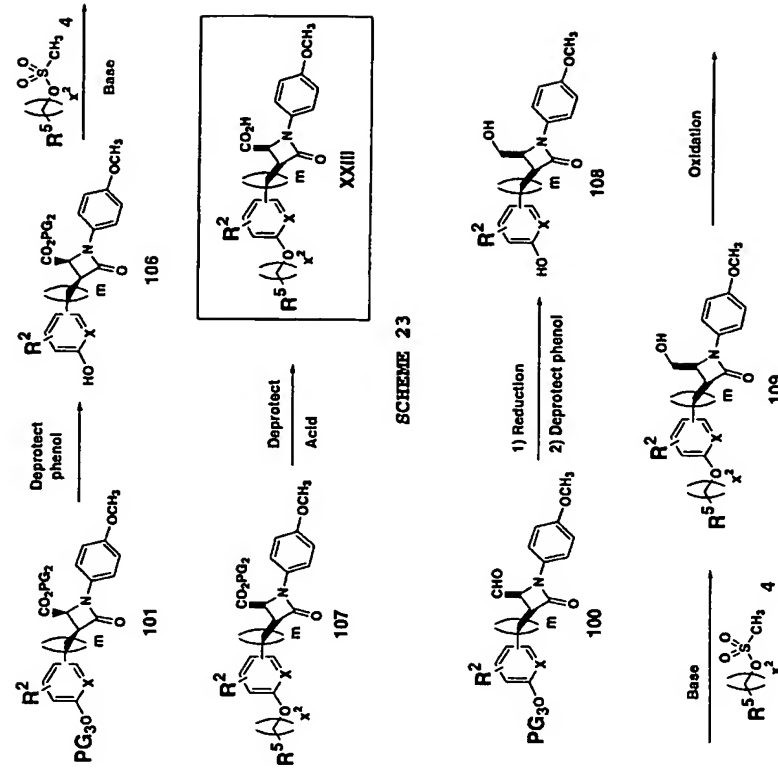
SCHEME 20B



SCHEME 21

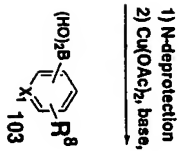
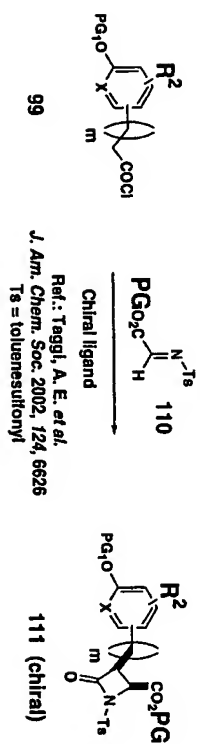


SCHEME 22

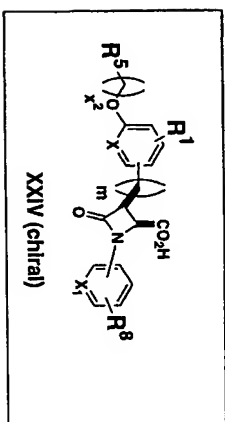


SCHEME 23

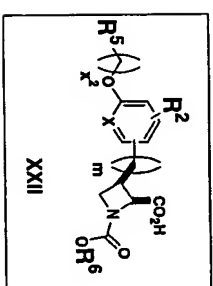
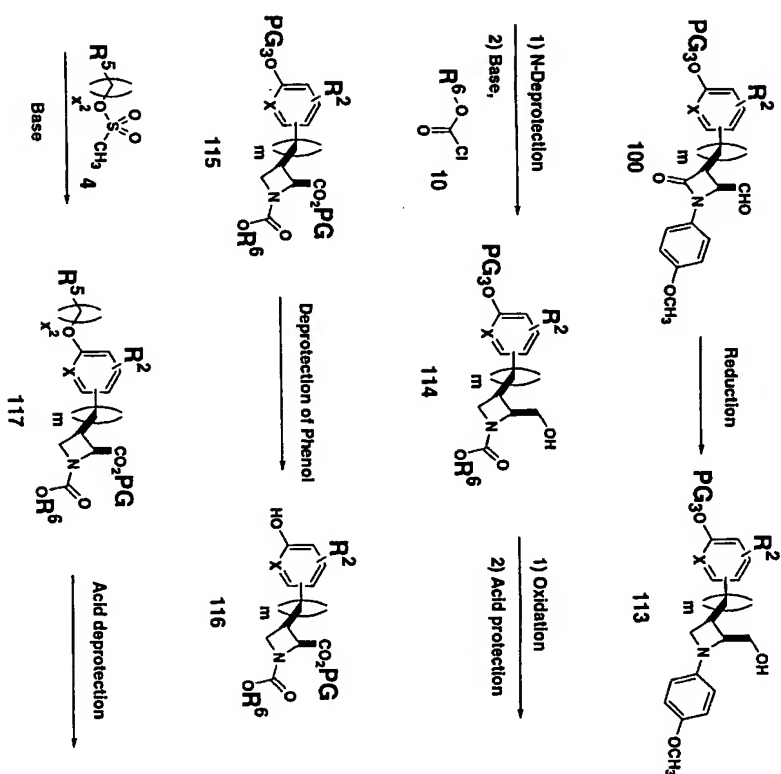
SCHEME 24



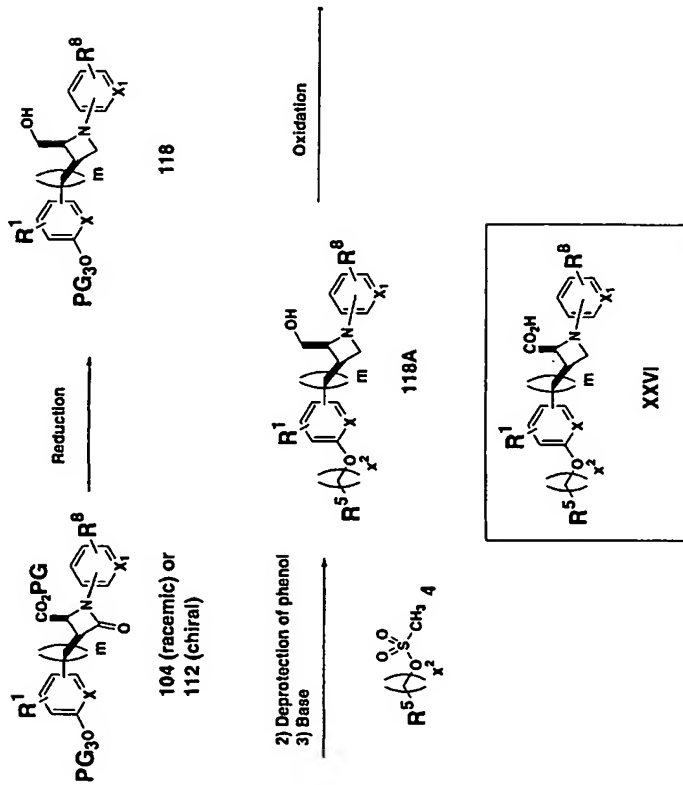
As for Scheme 22



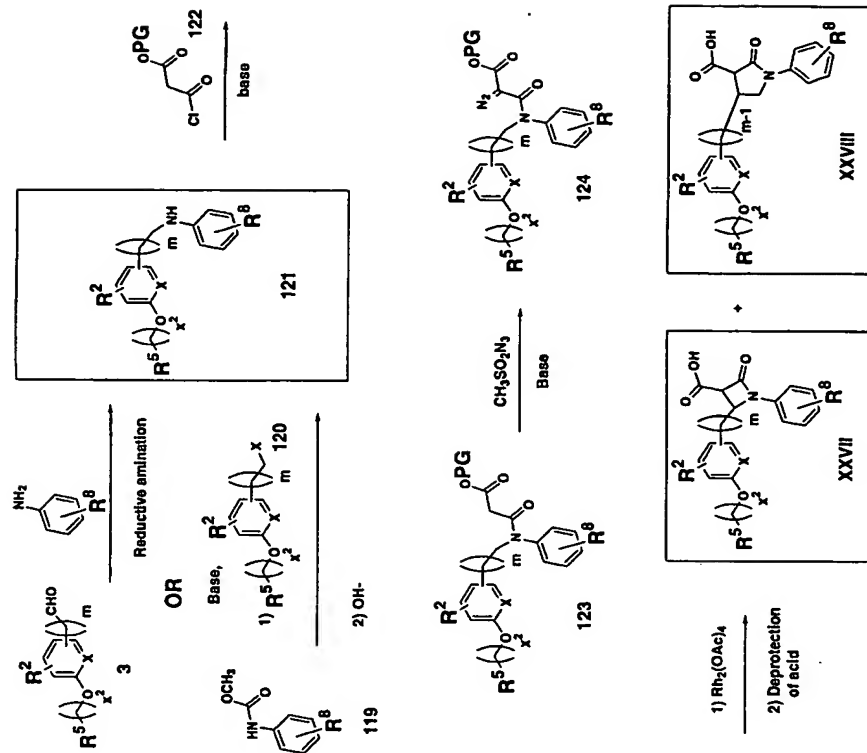
SCHEME 25



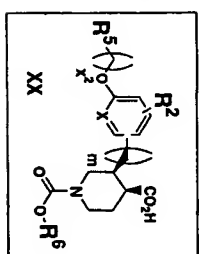
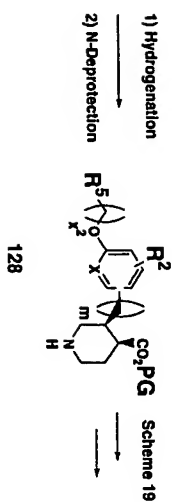
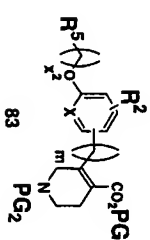
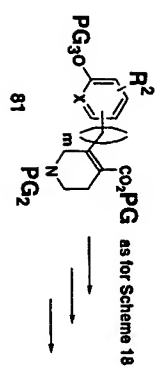
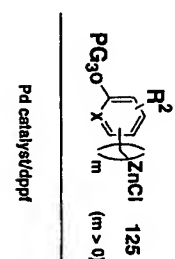
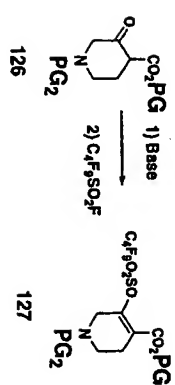
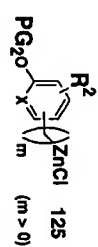
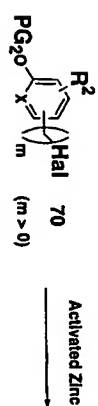
SCHEME 26



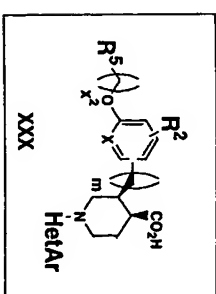
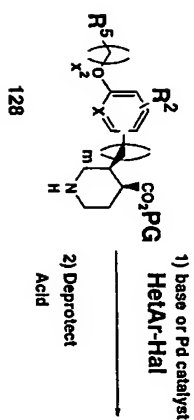
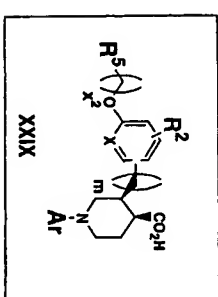
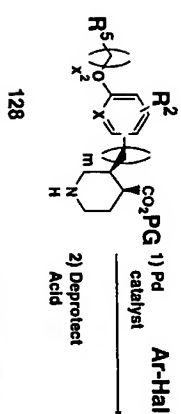
SCHEME 27



SCHEME 28

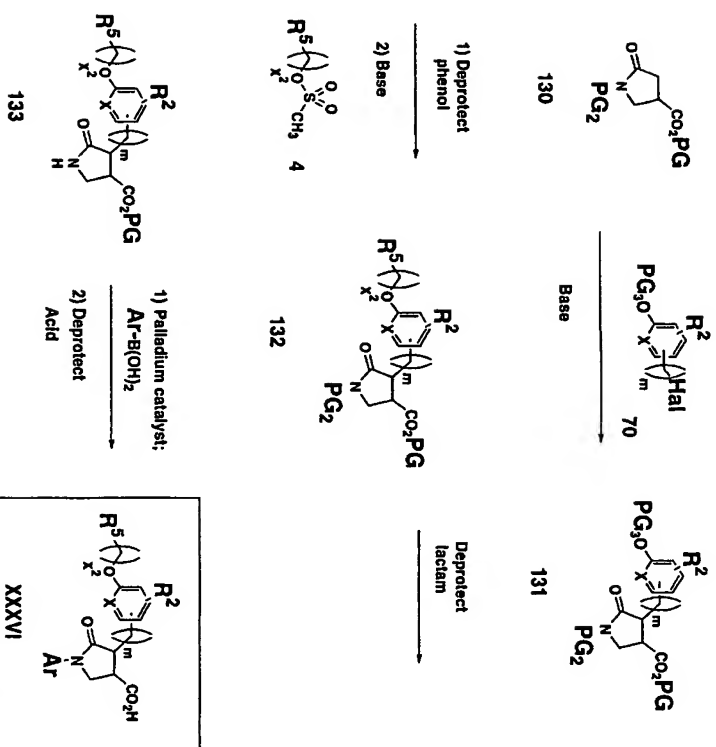


SCHEME 29

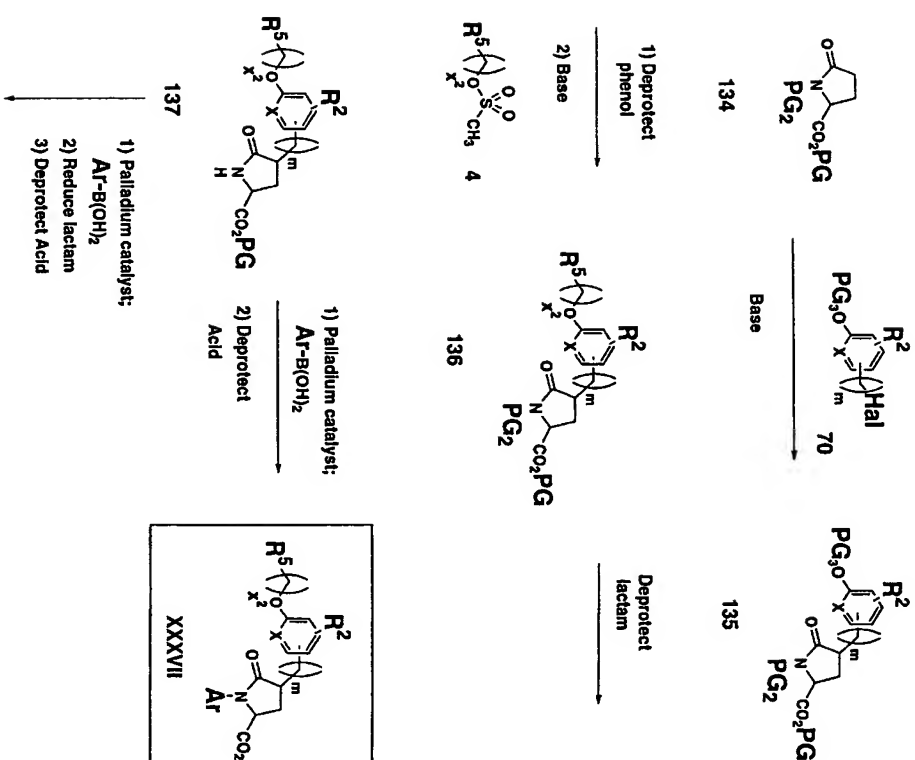


SCHEME 30



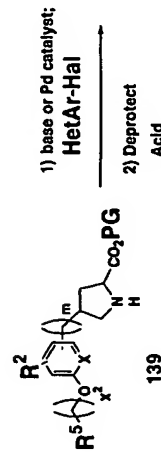
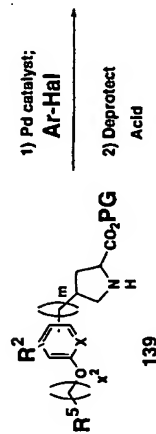
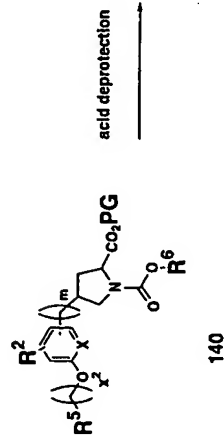
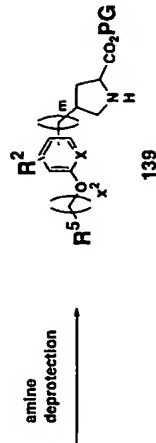
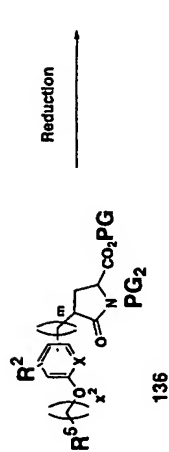


SCHEME 33

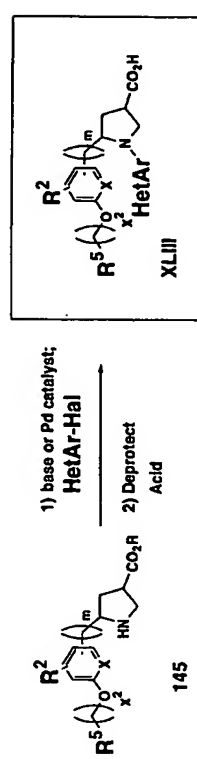
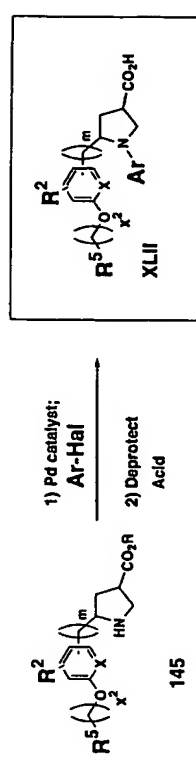
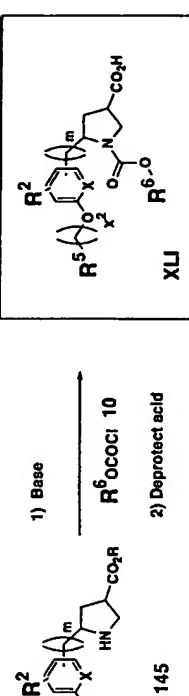
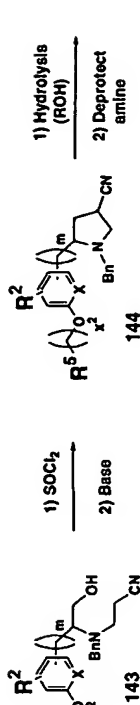
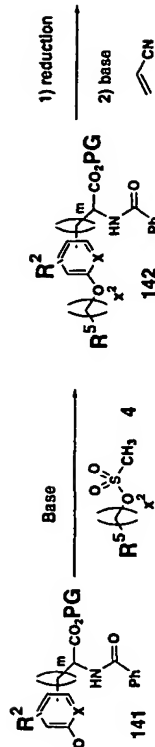


SCHEME 34

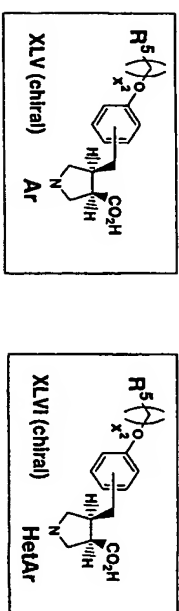
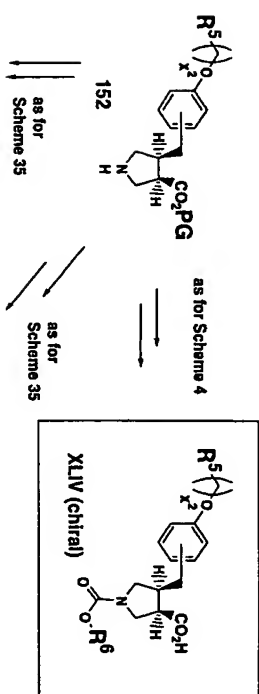
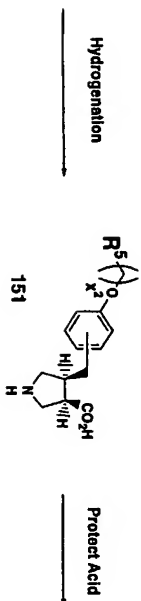
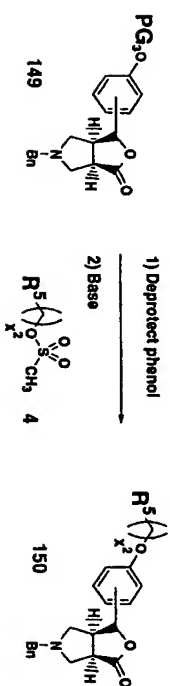
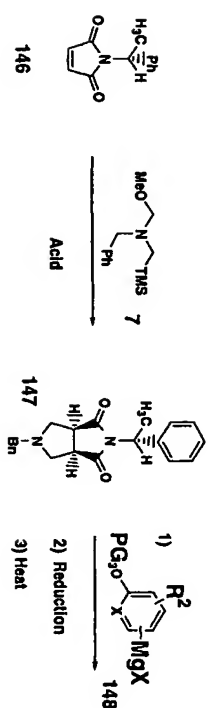




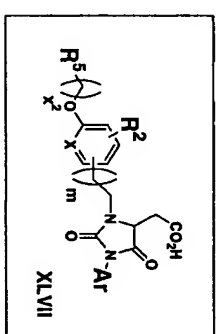
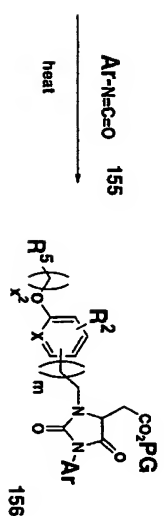
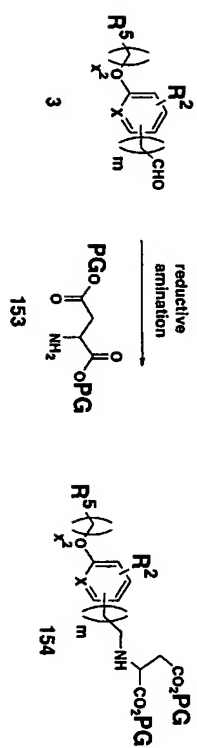
SCHEME 35



SCHEME 36

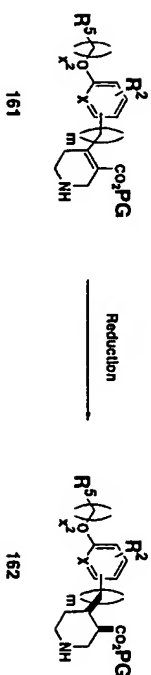


SCHEME 37



SCHEME 38

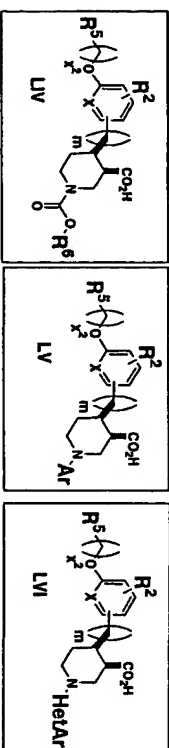




As for Scheme 37

As for Scheme 37

As for Scheme 37



SCHEME 41

In the above schemes, it will be seen that PG is a protecting group for a carboxylic acid. PG is a protecting group for an amine. PG is a protecting group for a phenol.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 20 carbons, preferably 1 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, and may optionally include an oxygen or nitrogen in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups

including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF<sub>3</sub>, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, hydroxyalkyl, acyl, heteroaryl, heteroaryloxy, cycloheteroalkyl, arylheteroaryl, arylalkoxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, heteroarylalkyl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio and/or any of the R<sup>3</sup> groups.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclical, bicyclic and tricyclic, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio and/or any of the substituents for alkyl.

The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 3 to 12 carbons, preferably 5 to 10 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups

- 80 -

alkylcarbonylamino or alkylcarbonyloxy; the alkyl substituent may be an alkylene moiety of 1 to 4 carbons which may be attached to one or two carbons in the  $(CH_2)_x$ .

$(\text{CH}_2)_1^x$ ,  $(\text{CH}_2)_2^x$ ,  $(\text{CH}_2)_3^x$ ,  $(\text{CH}_2)_4^x$ ,  $(\text{CH}_2)_5^x$ ,  $(\text{CH}_2)_6^x$ ,  $(\text{CH}_2)_7^x$ ,  $(\text{CH}_2)_8^x$ ,  $(\text{CH}_2)_m$ ,  $(\text{CH}_2)_n$ ,  $(\text{CH}_2)_p$ , or  $(\text{CH}_2)_q$  group to form a cycloalkyl group therewith.

Examples of  $(\text{CH}_2)_x$ ,  $(\text{CH}_2)_x^1$ ,  $(\text{CH}_2)_x^2$ ,  $(\text{CH}_2)_x^3$ ,  $(\text{CH}_2)_x^4$ ,  $(\text{CH}_2)_x^5$ ,  $(\text{CH}_2)_x^6$ ,  $(\text{CH}_2)_x^7$ ,  $(\text{CH}_2)_x^8$ ,  $(\text{CH}_2)_m$ ,  $(\text{CH}_2)_n$ ,  $(\text{CH}_2)_p$ ,  $(\text{CH}_2)_q$ , alkylene, alkenylene and alkynylene include

$$\begin{array}{l}
-\text{CH}=\text{CH}-\text{CH}_2-, \quad -\text{CH}_2\text{CH}=\text{CH}-, \quad -\text{C}\equiv\text{C}-\text{CH}_2-, \quad -\text{CH}_2-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-, \quad -\text{CH}=\text{C}- \\
-\text{CH}_2-\text{CH}_2-\text{CH}_2-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-, \quad -\text{CH}_2\text{C}\equiv\text{CCH}_2-, \quad -\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}=\text{CH}-\text{CH}_2-, \\
-(\text{CH}_2)_2-, \quad -(\text{CH}_2)_3-, \quad -(\text{CH}_2)_4-, \quad -(\text{CH}_2)_2-\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}-\text{CH}_2\text{CH}_2-, \quad -\text{CH}-\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}-,
\end{array}$$
$$\begin{array}{ccccccc}
 \begin{array}{c} \text{C}_2\text{H}_5 \\ | \\ -\text{CH}- \\ | \\ \text{C}_2\text{H}_5 \end{array} & , & \begin{array}{c} \text{H}_2\text{C} \\ | \\ -\text{CH}- \\ | \\ \text{CH}_2 \end{array} & , & \begin{array}{c} \text{CH}_2-\text{CH}=\text{CH}_2 \\ | \\ -\text{CH}- \\ | \\ \text{CH}_2 \end{array} & , & \begin{array}{c} \text{CH}_2-\text{CH}=\text{CH}_2 \\ | \\ -\text{CH}- \\ | \\ \text{CH}_2 \end{array} \\
 \begin{array}{c} \text{CH}_2-\text{CH}_2 \\ | \\ -\text{C}- \\ | \\ \text{CH}_2 \end{array} & , & \begin{array}{c} \text{H}_3\text{C} \\ | \\ -\text{C}-\text{CH}_2- \\ | \\ \text{CH}_3 \end{array} & , & -\text{CH}=\text{C}=\text{CH}- & , & -\text{CH}_2-\text{C}\equiv\text{C}- & , & -\text{CH}_2-\text{CH}-\text{CH}- \\
 & & & & & & & & \diagup \\
 & & & & & & & & \text{CH}
 \end{array}$$
$$\begin{array}{ccccccc} \text{---CHCHCH}_2\text{---} & , & \text{---CH}_2\text{---C(CH}_3)_2\text{---CH}_2\text{---} & , & \text{---(CH}_2)_5\text{---} & , & \text{---(CH}_2)_2\text{---C(CH}_3)_2\text{---} \\ | & & | & & & & | \\ \text{CH}_3 & & \text{CH}_3 & & & & \text{CH}_3 \\ & & & & & & \text{I} \\ & & & & & & \text{I} \\ & & & & & & \text{CH}_2\text{---} \\ & & & & & & | \\ & & & & & & \text{I} \end{array}$$
$$\begin{array}{c}
\text{CH}_3 \\
| \\
-\text{CH}_2-\text{CH}-\text{CH}-\text{CH}_2- \\
| \quad | \\
\text{CH}_3 \quad \text{CH}_3 \\
\text{CH}_3 \\
| \\
-\text{CH}_2-\text{CH}-\text{CH}_2-\text{CH}- \\
| \quad | \\
\text{CH}_3 \quad \text{CH}_3 \\
\text{CH}_3 \\
| \\
-\text{CH}-\text{CH}_2\text{CH}_2- \\
| \\
\text{CH}_3
\end{array}
, \quad
\begin{array}{c}
\text{OCH}_3 \\
| \\
-\text{CH}-\text{CH}_2\text{CH}_2- \\
| \\
\text{OCH}_3
\end{array}
, \quad
\begin{array}{c}
\text{OCH}_2\text{CH}_2- \\
| \\
-\text{OCH}_2\text{CH}_2- \\
| \\
-\text{CH}_2\text{NHCH}_2-
\end{array}
, \quad
\begin{array}{c}
\text{CH}_3 \\
| \\
-\text{CH}-\text{CH}_2\text{CH}_2- \\
| \\
\text{CH}_3
\end{array}$$

25

$$\begin{array}{c}
\text{CH}_3 \\
| \\
-\text{NHCH}_2\text{CH}_2- \\
| \\
\text{CH}_3
\end{array}
, \quad
\begin{array}{c}
(\text{CH}_2)_3 \\
| \\
-\text{CH}_2-\text{N}-\text{CH}_2- \\
| \\
\text{CH}_3
\end{array}
\quad \text{or} \quad
\begin{array}{c}
\text{CH}_3 \\
| \\
-\text{N}-\text{CH}_2\text{CH}_2- \\
| \\
\text{CH}_3
\end{array}$$

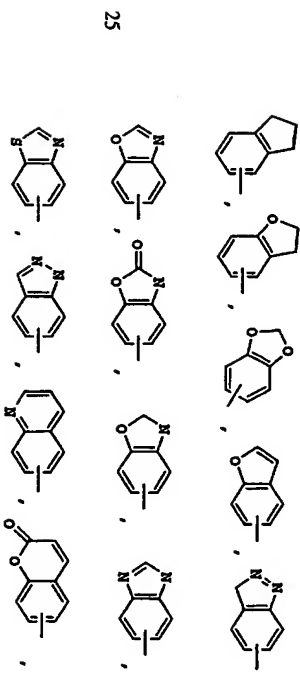
The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as  $\text{CF}_3$ , with chlorine or fluorine being preferred.

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

10        unless otherwise indicated, the term "aryl" or the  
group

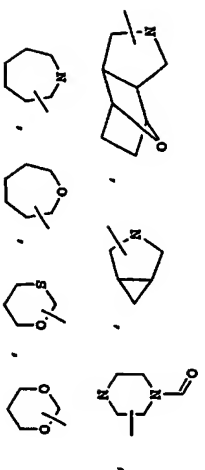


where Q is C, as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings for example



and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from



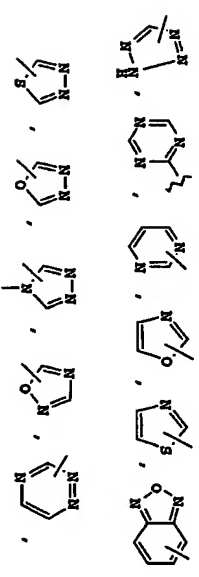
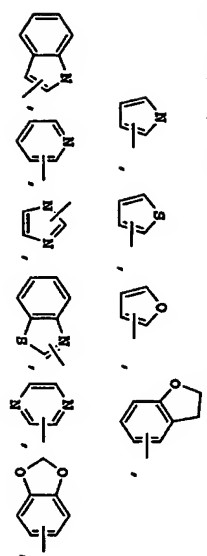


5 and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of of the substituents for alkyl or aryl set out herein. In addition, any of the cycloheteroalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

10 Unless otherwise indicated, the term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring including



15 where Q is N, which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as any of the the substituents for alkyl or aryl set out above. Examples of heteroaryl groups include the following:



5 and the like.

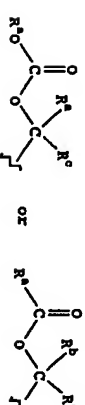
The term "cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a  $(CH_2)_p$  chain.

10 The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a  $-(CH_2)_p$  chain, alkylene or alkenylene as defined above.

15 The term "polyhaloalkyl" as used herein refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as  $CF_3CH_2$ ,  $CF_3$  or  $CF_3CF_2CH_2$ .

20 The term "polyhaloalkyloxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as  $CF_3CH_2O$ ,  $CF_3O$  or  $CF_3CF_2CH_2O$ .

25 The term "prodrug esters" as employed herein includes prodrug esters which are known in the art for carboxylic and phosphorus acid esters such as methyl, ethyl, benzyl and the like. Other prodrug ester examples of  $R^4$  include the following groups:





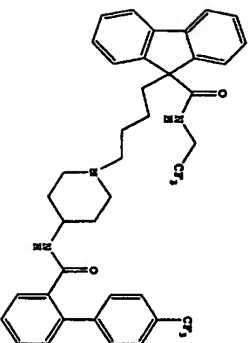


Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Application Serial No. 09/175,180 filed October 20, 1998, now U.S. Patent No. 5,962,440. Preferred are each of the preferred MTP inhibitors disclosed in each of the above patents and applications.

All of the above U.S. Patents and applications are incorporated herein by reference.

Most preferred MTP inhibitors to be employed in accordance with the present invention include preferred MTP inhibitors as set out in U.S. Patent Nos. 5,739,135 and 5,712,279, and U.S. Patent No. 5,760,246.

The most preferred MTP inhibitor is 9-[4-{(2-(2,2,2-trifluoroethoxy)benzoyl)amino}-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



The hypolipidemic agent may be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, atorvastatin disclosed in U.S. Patent Nos. 4,681,893,

5,273,995, 5,385,929 and 5,686,104, itavastatin (Nissan/Sankyo's nisvastatin (NR-104)) disclosed in U.S. Patent No. 5,011,930, Shionogi-Astra/Zeneca visastatin (2D-4522) disclosed in U.S. Patent No. 5,260,440, and related statin compounds disclosed in U.S. Patent No. 5,753,675, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No. 0,142,146 A2, and quinoline and pyridine derivatives disclosed in U.S. Patent No. 5,506,219 and 5,691,322.

In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

The squalene synthetase inhibitors suitable for use herein include, but are not limited to,  $\alpha$ -phosphonosulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphiny-1-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A.,

Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D.,  
Current Pharmaceutical Design, 2, 1-40 (1996).

In addition, other squalene synthetase inhibitors  
suitable for use herein include the terpenoid  
pyrophosphates disclosed by P. Ortiz de Montellano et al,  
J. Med. Chem., 1977, 20, 243-249, the farnesyl  
diphosphate analog A and presqualene pyrophosphate  
(PSQ-PP) analogs as disclosed by Corey and Volante, J.  
Am. Chem. Soc., 1976, 98, 1291-1293,  
10 phosphinylphosphonates reported by McClard, R.W. et al,  
J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by  
Capson, T.L., PhD dissertation, June, 1987, Dept. Med.  
Chem. U of Utah, Abstract, Table of Contents, pp 16, 17,  
40-43, 48-51, Summary.

15 Other hypolipidemic agents suitable for use herein  
include, but are not limited to, fibric acid derivatives,  
such as fenofibrate, gemfibrozil, clofibrate,  
bezafibrate, ciprofibrate, clonofibrate and the like,  
probucol, and related compounds as disclosed in U.S.  
20 Patent No. 3,674,836, probucol and gemfibrozil being  
preferred, bile acid sequestrants such as cholestyramine,  
colestipol and DEAE-Sephadex (Secholex®, Policexide®) and  
cholestegel (Sankyo/Geltex), as well as lipostabil  
(Rhône-Poulenc), Eisai E-5050 (an N-substituted  
25 ethanolamine derivative), imanixil (HOE-402),  
tetrahydrolipstatin (THL), istigmastanylphos-  
phorylcholine (SPC, Roche), aminocyclodextrin (Tanabe  
Seiyoku), Ajinomoto AJ-814 (azulene derivative),  
melinamide (Sumitomo), Sandoz 58-035, American Cyanamid  
30 CL-277,082 and CL-283,546 (disubstituted urea  
derivatives), nicotinic acid (niacin), acipimox, acifran,  
neomycin, p-aminosalicylic acid, aspirin,  
poly(diallylmethylamine) derivatives such as disclosed in  
U.S. Patent No. 4,759,923, quaternary amine  
35 poly(diallyldimethylammonium chloride) and ionenes such  
as disclosed in U.S. Patent No. 4,027,009, and other  
known serum cholesterol lowering agents.

The hypolipidemic agent may be an ACAT inhibitor  
such as disclosed in, Drugs of the Future 24, 9-15  
(1999), (Avasimibe); "The ACAT inhibitor, CL-1011 is  
effective in the prevention and regression of aortic  
5 fatty streak area in hamsters", Nicolosi et al,  
Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85;  
"The pharmacological profile of FCE 27677: a novel ACAT  
inhibitor with potent hypolipidemic activity mediated by  
selective suppression of the hepatic secretion of  
10 ApoB100-containing lipoprotein", Ghiselli, Giancarlo,  
Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a  
bioavailable alkylsulfanyl-diphenylimidazole ACAT  
inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett.  
(1996), 6(1), 47-50; "ACAT inhibitors: physiologic  
15 mechanisms for hypolipidemic and anti-atherosclerotic  
activities in experimental animals", Krause et al,  
Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Manfred  
A., Inflammation: Mediators Pathways (1995), 173-98,  
Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors:  
20 potential anti-atherosclerotic agents", Sliksovic et al,  
Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of  
acyl-CoA:cholesterol O-acyl transferase (ACAT) as  
hypocholesterolemic agents. 6. The first water-soluble  
ACAT inhibitor with lipid-regulating activity. Inhibitors  
25 of acyl-CoA:cholesterol acyltransferase (ACAT). 7.  
Development of a series of substituted N-phenyl-N'-{(1-  
phenylcyclopentyl)methyl}ureas with enhanced  
hypocholesterolemic activity", Stout et al, Chemtracts:  
Org. Chem. (1995), 8(6), 359-62, or TS-962 (Taisho  
30 Pharmaceutical Co. Ltd) as well as F-1394, CS-505, F-  
12511, HL-004, K-10085 and VIC-C8-434.

The hypolipidemic agent may be an upregulator of  
LDL receptor activity such as MD-700 (Taisho  
Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

35 The hypolipidemic agent may be a cholesterol  
absorption inhibitor preferably Schering-Plough's  
SCH48461 (ezetimibe) as well as those disclosed in

Atherosclerosis 115, 45-63 (1995) and J. Med. Chem. 41, 973 (1998).

The hypolipidemic agent may be an ileal Na<sup>+</sup>/bile acid cotransporter inhibitor such as disclosed in Drugs of the Future, 24, 425-430 (1999).

The lipid-modulating agent may be a cholesterol ester transfer protein (CEP) inhibitor such as Pfizer's CP 529,414 as well as those disclosed in WO/0038722 (i.e. (torcetrapib) and in EP 818448 (Bayer) and EP 992496 and Pharmacia's SC-744 and SC-795, as well as CETI-1 and JTT-705.

The ATP citrate lyase inhibitor which may be employed in the combination of the invention may include, for example, those disclosed in U.S. Patent No. 5,447,954.

The other lipid agent also includes a phytoestrogen compound such as disclosed in WO 00/30665 including isolated soy bean protein, soy protein concentrate or soy flour as well as an isoflavone such as genistein, daidzein, glycitein or equol, or phytoosterols, phytostanol or tocotrienol as disclosed in WO 2000/015201; a beta-lactam cholesterol absorption inhibitor such as disclosed in EP 675714; an HDL upregulator such as an LXR agonist, a PPAR alpha agonist and/or an FXR agonist; a PPAR delta agonist (e.g. GW-501516, ref: Oliver, Jr., W. R., et. al, Proc. Nat. Acad. Sci. USA, 2001, 98, 5306-5311), an LDL catabolism promoter such as disclosed in EP 1022272; a sodium-proton exchange inhibitor such as disclosed in DE 19622222; an LDL-receptor inducer or a steroidal glycoside such as disclosed in U.S. Patent No. 5,698,527 and GB 2304106; an anti-oxidant such as beta-carotene, ascorbic acid,  $\alpha$ -tocopherol or retinol as disclosed in WO 94/15592 as well as Vitamin C and an antihomocysteine agent such as folic acid, a folate, Vitamin B6, Vitamin B12 and Vitamin E; isoniazid as disclosed in WO 97/35576; a cholesterol absorption inhibitor, an HMG-CoA synthase inhibitor, or a

lanosterol demethylase inhibitor as disclosed in WO 97/48701; a PPAR  $\delta$  agonist for treating dyslipidemia; or a sterol regulating element binding protein-1 (SREBP-1) as disclosed in WO 2000/050574, for example, a sphingolipid, such as ceramide, or neutral sphingomyelinase (N-SMase) or fragment thereof.

The above-mentioned U.S. patents are incorporated herein by reference. The amounts and dosages employed will be as indicated in the Physician's Desk Reference and/or in the patents set out above.

The compounds of formula I of the invention will be employed in a weight ratio to the hypolipidemic agent (were present), within the range from about 500:1 to about 1:500, preferably from about 100:1 to about 1:100.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

The dosages and formulations for the hypolipidemic agent will be as disclosed in the various patents and applications discussed above.

The dosages and formulations for the other hypolipidemic agent to be employed, where applicable, will be as set out in the latest edition of the Physicians' Desk Reference.

For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg to about 500 mg and preferably from about 0.1 mg to about 100 mg, one to four times daily.

A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2 to about 400 mg, and more preferably from about 5 to about 250 mg, one to four times daily.

For oral administration, a satisfactory result may be obtained employing an HMG CoA reductase inhibitor, for

example, pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin or rosuvastatin in dosages employed as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 0.5 to about 80 mg, and more preferably from about 1 to about 40 mg.

A preferred oral dosage form, such as tablets or capsules will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

The hypolipidemic agent may also be a lipoxxygenase inhibitor including a 15-lipoxxygenase (15-LO) inhibitor such as benzimidazole derivatives as disclosed in WO 97/12615, 15-LO inhibitors as disclosed in WO 97/12613, isothiazolones as disclosed in WO 96/38144, and 15-LO inhibitors as disclosed by Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxxygenase inhibitor lacking significant antioxidant properties", Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, "15-Lipoxxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 1999, 5, 11-20.

The compounds of formula I and the hypolipidemic agent may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in

single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

The preferred hypolipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or rosuvastatin as well as niacin and/or cholestergel.

The other antidiabetic agent which may be

optionally employed in combination with the compound of formula I may be 1,2,3 or more antidiabetic agents or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, or other antidiabetic agents preferably having a mechanism of action different from the compounds of formula I of the invention, which may include biguanides, sulfonyl ureas, glucosidase inhibitors, PPAR $\gamma$  agonists such as thiazolidinediones, PPAR $\alpha$  agonists such as fibric acid derivatives, PPAR $\delta$  agonists or antagonists, PPAR $\alpha/\gamma$  dual agonists, AP2 inhibitors, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors, glycogen phosphorylase inhibitors, glucagon-like peptide-1 (GLP-1), PTP-1B (protein tyrosine phosphatase-1B) inhibitors, 11 $\beta$ -HSD 1 (11 $\beta$ -hydroxysteroid dehydrogenase 1) inhibitors and/or meglitinides, as well as insulin.

The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl.

Where the antidiabetic agent is a biguanide, the compounds of structure I will be employed in a weight ratio to biguanide within the range from about 0.001:1 to about 10:1, preferably from about 0.01:1 to about 5:1.

The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic

agents which act on the ATP-dependent channel of the  $\beta$ -cells, with glyburide and glipizide being preferred, which may be administered in the same or in separate oral dosage forms.

- 5 The compounds of structure I will be employed in a weight ratio to the sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.02:1 to about 5:1.

The oral antidiabetic agent may also be a

- 10 glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in the same or in a separate oral dosage forms.

- 15 The compounds of structure I will be employed in a weight ratio to the glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.05:1 to about 10:1.

The compounds of structure I may be employed in combination with a PPAR  $\gamma$  agonist such as a

- 20 thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as rosiglitazone (Glaxo SmithKline), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Wellcome's Gl-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MT/J&J), JTY-501 (JPNP/P&U), L-895645 (Merck), R-119702 (Sankyo/ML), NN-2344 or balaglitazone (Dr. Reddy/NN), or YM-440 (Yamanouchi), preferably rosiglitazone and pioglitazone.

- 30 The compounds of structure I will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.05 to about 10:1.

- 35 The sulfonyl urea and thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with the compounds of structure I.

- The compounds of structure I may also be employed in combination with a antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference), as well as AC2993 (Amylin) and LY-315902 (lilly), which may be administered via injection, intranasal, inhalation or by transdermal or buccal devices.

- 10 Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipizide, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may be employed in formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference (PDR).

- 15 Where present, metformin or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day which may be administered in single or divided doses one to four times daily.

- 20 Where present, the thiazolidinedione anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

- 25 Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

- Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701 (Theratech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

- 30 The other antidiabetic agent may also be a PPAR  $\alpha/\gamma$  dual agonist such as AZ-242/tesaglitazar (Astra/Zeneca; as described in B. Ljung et. al., *J. Lipid Res.*, 2002, 43, 1855-1863), GW-409544 (Glaxo-Wellcome), KRP-297/MK-767 (Kyorin/Merck; as described in:

- 35

K. Vajima et. al., *Am. J. Physiol. Endocrinol. Metab.*, 2003, 284: E966-E971) as well as those disclosed by Murakami et al., "A Novel Insulin Sensitizer Acts As a Coligand for Peroxisome Proliferation - Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", *Diabetes* 47, 1841-1847 (1998) or the compounds (from Bristol-Myers Squibb) described in US patent 6414002.

The antidiabetic agent may be an SGLT2 inhibitor such as disclosed in U.S. provisional application No. 60/158,773, filed October 12, 1999 (attorney file LA49), employing dosages as set out therein. Preferred are the compounds designated as preferred in the above application.

The antidiabetic agent may be an ap2 inhibitor such as disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and in U.S. provisional application No. 60/127,745, filed April 5, 1999 (attorney file LA27\*), employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

The antidiabetic agent may be a DP4 (Dipeptidyl peptidase IV) inhibitor such as disclosed in Provisional Application 60/188,555 filed March 10, 2000 (attorney file LA50), WO99/38501, WO99/46272, WO99/67279 (PROBIODRUG), WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethylamino]acetyl]-2-cyano-(S)-pyrrolidine] (Novartis) (preferred) as disclosed by Hughes et al., *Biochemistry*, 38(36), 11597-11603, 1999, TSL-225 (tryptophyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (disclosed by Yamada et al., *Bioorg. & Med. Chem. Lett.* 8 (1998) 1537-1540, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al., *Bioorg. & Med. Chem. Lett.*, Vol. 6, No. 22, pp 1163-1166 and

2745-2748 (1996) employing dosages as set out in the above references.

The meglitinide which may optionally be employed in combination with the compound of formula I of the invention may be repaglinide, nateglinide (Novartis) or KAD1229 (PF/Kissei), with repaglinide being preferred.

The compound of formula I will be employed in a weight ratio to the meglitinide, PPAR  $\gamma$  agonist, PPAR  $\alpha/\gamma$  dual agonist, ap2 inhibitor, DP4 inhibitor or SGLT2 inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.05 to about 10:1.

The other type of therapeutic agent which may be optionally employed with a compound of formula I may be 1, 2, 3 or more of an anti-obesity agent including a melanocortin receptor (MC4R) agonist, a melanin-concentrating hormone receptor (MCHR) antagonist, a growth hormone secretagogue receptor (GHSR) antagonist, an orexin receptor antagonist, a CCK (cholecystokinin) agonist, a GIP-1 agonists, NPY1 or NPY5 antagonist, a corticotropin releasing factor (CRF) antagonist, a histamine receptor-3 (H3) modulator, a PPAR $\gamma$  modulator, a PPAR $\delta$  modulator, a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a serotonin receptor agonist (e.g. BVT-933), an ap2 inhibitor, a thyroid receptor agonist and/or an anorectic agent.

The beta 3 adrenergic agonist which may be optionally employed in combination with a compound of formula I may be AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, with AJ9677, L750,355 and CP331648 being preferred.

The lipase inhibitor which may be optionally employed in combination with a compound of formula I may be orlistat or ATL-962 (Alizyme), with orlistat being preferred.

The serotonin (and dopamine) reuptake inhibitor which may be optionally employed in combination with a compound of formula I may be sibutramine, topiramate (Johnson & Johnson) or CNTF/axokine (Regeneron), with sibutramine and topiramate being preferred.

The thyroid receptor agonist which may be optionally employed in combination with a compound of formula I may be a thyroid receptor ligand as disclosed in WO97/21993 (U. Cal SF), WO99/00353 (KaroBio), GB98/284425 (KaroBio), and U.S. Provisional Application 60/183,223 filed February 17, 2000, with compounds of the KaroBio applications and the above U.S. provisional application being preferred.

The anorectic agent which may be optionally employed in combination with a compound of formula I may be fenfluramine, dexfenfluramine, fluvoxamine, fluoxetine, paroxetine, sertraline, chlorphentermine, clorofex, clortermine, piclorex, sibutramine, dexamphetamine, phentermine, phenylpropanolamine or mazindol. Other anorectic agents which may be optionally employed in combination with a compound of formula I include CNTF (ciliary neurotrophic factor)/Axokine (Regeneron), BDNF (brain-derived neurotrophic factor), leptin or cannabinoid receptor antagonists, such as SR-141716/rimonabant (Sanofi) or SLV-319 (Solvay).

The various anti-obesity agents described above may be employed in the same dosage form with the compound of formula I or in different dosage forms, in dosages and regimens as generally known in the art or in the PDR.

The antihypertensive agents which may be employed in combination with the compound of formula I of the invention include ACE inhibitors, angiotensin II receptor antagonists, NEP/ACE inhibitors, as well as calcium channel blockers,  $\beta$ -adrenergic blockers and other types of antihypertensive agents including diuretics.

The angiotensin converting enzyme inhibitor which may be employed herein includes those containing a

mercaptop (-S-) moiety such as substituted proline derivatives, such as any of those disclosed in U.S. Pat. No. 4,046,889 to Ondetti et al mentioned above, with captopril, that is, 1-[(1S)-3-mercaptop-2-methylpropionyl]-L-proline, being preferred, and

mercaptopacyl derivatives of substituted prolines such as any of those disclosed in U.S. Pat. No. 4,316,906 with zofenopril being preferred.

Other examples of mercapto containing ACE inhibitors that may be employed herein include rentiapril (fentiapril, Santen) disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983); as well as pivopril and VS980.

Other examples of angiotensin converting enzyme inhibitors which may be employed herein include any of those disclosed in U.S. Pat. No. 4,374,829 mentioned above, with N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline, that is, enalapril, being preferred, any of the phosphonate substituted amino or imino acids or salts disclosed in U.S. Pat. No. 4,452,790 with (S)-1-[6-amino-2-[[hyatroxy-(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline or (ceronapril) being preferred, phosphinylalkanyl prolines disclosed in U.S. Pat. No. 4,168,267 mentioned above with fosinopril being preferred, any of the phosphinylalkanyl substituted prolines disclosed in U.S. Pat. No. 4,337,201, and the phosphonamides disclosed in U.S. Pat. No. 4,432,971 discussed above.

Other examples of ACE inhibitors that may be employed herein include Beecham's BRU 36,378 as disclosed in European Patent Application Nos. 80822 and 60668; Chugal's MC-838 disclosed in C.A. 102:72588v and Jap. J. Pharmacol. 40:373 (1986); Ciba-Geigy's CGS 14824 (3-[[1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed in U.K. Patent No. 2103614 and CGS 16,617 (3(S)-[[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid])



disclosed in U.S. Pat. No. 4,473,575; cetapril (alacepril, Dainippon) disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986); ramipril (Hoechst) disclosed in Euro. Patent No. 79-022 and Curr. Ther. Res. 40:74 (1986); Ru 44570 (Hoechst) disclosed in

5 Arzneimittelforschung 34:1254 (1985), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987); R 31-2201 (Hoffman-LaRoche) disclosed in

10 FEBS Lett. 165:201 (1984); lisinopril (Merck), indalaprill (delapril) disclosed in U.S. Pat. No. 4,385,051;

indolapril (Schering) disclosed in J. Cardiovasc.

Pharmacol. 5:643, 655 (1983), spirapril (Schering)

disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5):173

(1986); perindopril (Servier) disclosed in Eur. J. clin.

15 Pharmacol. 31:519 (1987); quinapril (Warner-Lambert)

disclosed in U.S. Pat. No. 4,344,949 and CI925 (Warner-

Lambert) ([3S-[2(R\*(R\*))3R(\*)]-2-[2-[(1-(ethoxy-

carbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-

tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid

20 HCl) disclosed in Pharmacologist 26:243, 266 (1984), WY-

44221 (Wyeth) disclosed in J. Med. Chem. 26:394 (1983).

Preferred ACE inhibitors are captopril, fosinopril,

enalapril, lisinopril, quinapril, benazepril, fentiapril,

ramipril and moexipril.

NEP/ACE inhibitors may also be employed herein in

25 that they possess neutral endopeptidase (NEP) inhibitory

activity and angiotensin converting enzyme (ACE)

inhibitory activity. Examples of NEP/ACE inhibitors

suitable for use herein include those disclosed in U.S.

30 Pat. No.s. 5,362,727, 5,366,973, 5,225,401, 4,722,810,

5,223,516, 4,749,688, U.S. Patent. No. 5,552,397, U.S.

Pat. No. 5,504,080, U.S. Patent No. 5,612,359, U.S. Pat.

No. 5,525,723, European Patent Application 0599,444,

0481,522, 0599,444, 0595,610, European Patent Application

35 0534363A2, 534,396 and 534,492, and European Patent

Application 0629627A2.

Preferred are those NEP/ACE inhibitors and dosages thereof which are designated as preferred in the above patents/applications which U.S. patents are incorporated herein by reference; most preferred are omapatrilat, BMS

5 189,921 ([S-(R\*(R\*))]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat)) and CGS 30440.

The angiotensin II receptor antagonist (also

referred to herein as angiotensin II antagonist or AII

10 antagonist) suitable for use herein includes, but is not

limited to, irbesartan, losartan, valsartan, candesartan,

telmisartan, tasosartan or eprosartan, with irbesartan,

losartan or valsartan being preferred.

A preferred oral dosage form, such as tablets or

15 capsules, will contain the ACE inhibitor or AII

antagonist in an amount within the range from about 0.1 to

about 500 mg, preferably from about 5 to about 200 mg and

more preferably from about 10 to about 150 mg.

For parenteral administration, the ACE inhibitor,

20 angiotensin II antagonist or NEP/ACE inhibitor will be

employed in an amount within the range from about 0.005

mg/kg to about 10 mg/kg and preferably from about 0.01

mg/kg to about 1 mg/kg.

Where a drug is to be administered intravenously,

25 it will be formulated in conventional vehicles, such as

distilled water, saline, Ringer's solution or other

conventional carriers.

It will be appreciated that preferred dosages of

ACE inhibitor and AII antagonist as well as other

30 antihypertensives disclosed herein will be as set out in

the latest edition of the Physician's Desk Reference

(PDR).

Other examples of preferred antihypertensive agents

suitable for use herein include omapatrilat (Vanlev®)

35 amlodipine besylate (Norvasc®), prazosin HCl

(Minipress®), verapamil, nifedipine, nadolol, diltiazem,

felodipine, nisoldipine, isradipine, nicardipine,

atenolol, carvedilol, sotalol, terazosin, doxazosin, propranolol, and clonidine HCl (Catapres®).

Diuretics which may be employed in combination with compounds of formula I include hydrochlorothiazide, torasemide, furosemide, spironolactone, and indapamide.

Antiplatelet agents which may be employed in combination with compounds of formula I of the invention include aspirin, clopidogrel, ticlopidine, dipyridamle, abciximab, tirofiban, eptifibatide, anagrelide, and ifetroban, with clopidogrel and aspirin being preferred.

The antiplatelet drugs may be employed in amounts as indicated in the PDR. Ifetroban may be employed in amounts as set out in U.S. Patent No. 5,100,889.

Antiosteoporosis agents suitable for use herein in combination with the compounds of formula I of the invention include parathyroid hormone or bisphosphonates, such as MK-217 (alendronate) (Fosamax®). Dosages employed will be as set out in the PDR.

In carrying out the method of the invention, a pharmaceutical composition will be employed containing the compounds of structure I, with or without another therapeutic agent, in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered to mammalian species including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations. The dose for adults is preferably between 50 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

A typical capsule for oral administration contains compounds of structure I (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed

through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectable preparation is produced by aseptically placing 250 mg of compounds of structure I into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

The following abbreviations are employed in the Examples:

- 5 Ph = phenyl  
Bn = benzyl  
t-Bu = tertiary butyl  
Me = methyl  
Et = ethyl
- 10 TMS = trimethylsilyl  
TMSN<sub>3</sub> = trimethylsilyl azide  
TMSCHN<sub>2</sub> = trimethylsilyl diazomethane  
TBS = tert-butyltrimethylsilyl  
TBDPS = tert-butyl-diphenylsilyl  
15 FMOC = fluorenylmethoxycarbonyl  
Boc = tert-butoxycarbonyl  
Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl  
THF = tetrahydrofuran  
Et<sub>2</sub>O = diethyl ether  
20 hex = hexanes  
EtOAc = ethyl acetate  
DMF = dimethyl formamide  
MeOH = methanol  
EtOH = ethanol
- 25 i-PrOH = IPA = isopropanol  
DMSO = dimethyl sulfoxide  
DME = 1,2 dimethoxyethane  
DCE = 1,2 dichloroethane  
HMPA = hexamethyl phosphoric triamide
- 30 HOAc or AcOH = acetic acid  
TFA = trifluoroacetic acid  
PTSA = pTSA = para-toluenesulfonic acid  
i-Pr<sub>3</sub>NET = diisopropylethylamine  
Et<sub>3</sub>N = TEA = triethylamine  
35 Et<sub>2</sub>NH = diethylamine  
NPM = N-methyl morpholine

- DMAP = 4-dimethylaminopyridine  
NaBH<sub>4</sub> = sodium borohydride  
NaBH(OAc)<sub>3</sub> = sodium triacetoxyborohydride  
DIBALH = diisobutyl aluminum hydride  
5 LiAlH<sub>4</sub> = lithium aluminum hydride  
n-BuLi = n-butyllithium  
Pd/C = palladium on carbon  
PtO<sub>2</sub> = platinum oxide  
KOH = potassium hydroxide  
10 NaOH = sodium hydroxide  
LiOH = lithium hydroxide  
K<sub>2</sub>CO<sub>3</sub> = potassium carbonate  
NaHCO<sub>3</sub> = sodium bicarbonate  
H<sub>2</sub>SO<sub>4</sub> = sulfuric acid  
15 KHSO<sub>4</sub> = potassium hydrogen phosphate  
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene  
EDC (or EDC.HCl) or EDCI (or EDCI.HCl) or EDAC = 3-ethyl-3'-(dimethylamino)propyl-carbodiimide hydrochloride (or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
20 hydrochloride)  
HOBT or HOBT.H<sub>2</sub>O = 1-hydroxybenzotriazole hydrate  
HOAT = 1-Hydroxy-7-azabenzotriazole  
BOP reagent = benzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluorophosphate  
25 NaN(TMS)<sub>2</sub> = sodium hexamethyldisilazide or sodium bis(trimethylsilyl)amide  
Ph<sub>3</sub>P = triphenylphosphine  
Pd(OAc)<sub>2</sub> = Palladium acetate  
(Ph<sub>3</sub>P)<sub>4</sub>Pd<sup>0</sup> = tetrakis triphenylphosphine palladium  
30 DEAD = diethyl azodicarboxylate  
DIAD = diisopropyl azodicarboxylate  
Cbz-Cl = benzyl chloroformate  
CAN = ceric ammonium nitrate  
SiO<sub>2</sub> = silica gel  
35 SAX = Strong Anion Exchanger

SCX = Strong Cation Exchanger

Ar = argon

N<sub>2</sub> = nitrogen

min = minute(s)

5 h or hr = hour(s)

L = liter

mL = milliliter

μL = microliter

μM = micromolar

10 g = gram(s)

mg = milligram(s)

mol = moles

mmol = millimole(s)

meq = milliequivalent

15 RT = room temperature

sat or sat'd = saturated

aq. = aqueous

TLC = thin layer chromatography

HPLC = high performance liquid chromatography

20 LC/MS = high performance liquid chromatography/mass spectrometry

MS or Mass Spec = mass spectrometry

NMR = nuclear magnetic resonance

NMR spectral data: s = singlet; d = doublet; m =

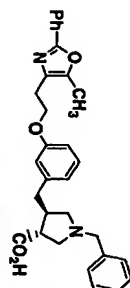
25 multiplet; br = broad; t = triplet

mp = melting point

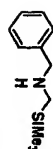
ee = enantiomeric excess

30 The following Examples represent preferred embodiments of the invention.

### Example 1

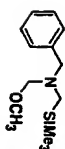


5 A.



A solution of benzylamine (8.9 mL; 82 mmol) and chloromethyltrimethylsilane (5.0 g; 41 mmol) in MeCN (100 mL) was heated at reflux for 16 h. The reaction was cooled to RT, filtered, and the filtrate was concentrated in vacuo to a volume of ~30 mL. H<sub>2</sub>O (100 mL) was added and the mixture was extracted with hexane (2 x 20 mL). The combined organic extracts were washed with H<sub>2</sub>O (3 x 20 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part A compound (7.70 g; 49%) as an oil.

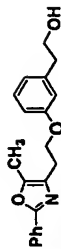
B.



20 To a 0°C solution of formaldehyde (4.6 g of a 37% aqueous solution; 55.7 mmol) and 1N aqueous NaOH (5 drops) was added dropwise Part A compound (7.70 g; 39.8 mmol). After the mixture had been stirred at 0°C for 10 min, MeOH (4 mL) was added, followed by K<sub>2</sub>CO<sub>3</sub> (4.0 g). The mixture was allowed to warm to RT and stirred at RT for 1 h. The organic phase was separated, more K<sub>2</sub>CO<sub>3</sub> (2.0 g) was added, and the reaction was stirred at RT for 12 h. Et<sub>2</sub>O (20 mL) was then added to the mixture, which was filtered and the filtrate was concentrated in vacuo. The

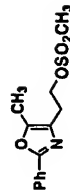
residual oil was distilled at reduced pressure (0.5 mm Hg; 80°C) to give Part B compound (4.67 g; 49%) as an oil.

5 C.



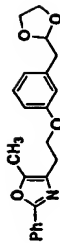
A mixture of 3-hydroxy phenylethanol (4.0 mg; 28 mmol), the mesylate Example 23 Part A compound (8.0 g; 28 mmol)

10 mmol)



and K<sub>2</sub>CO<sub>3</sub> (15.0 g; 110 mmol) in MeCN (150 mL) was stirred at 90°C for 5 h. At this point LC/MS showed that the reaction was complete. The reaction was cooled to RT, solids were filtered off, and the filtrate was diluted with EtOAc (100 mL). The solution was successively washed with aqueous 1 M HCl (10 mL), 1 M NaOH (10 mL) and H<sub>2</sub>O (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 2:1 hex:EtOAc) to give Part C compound (8.7 g; 96%) as an oil.

D.



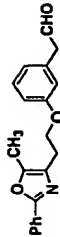
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To a solution of Part C compound (4.0 g; 12.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) were added Florisil™ (8.0 g), pyridinium chlorochromate (4.0 g; 19 mmol) and the reaction was stirred at RT for 3 h. The mixture was then diluted with anhydrous Et<sub>2</sub>O (200 mL) and filtered. The chromium solid wastes were washed with additional Et<sub>2</sub>O (3 x 100 mL); the combined organic filtrates were

concentrated in vacuo to give the very crude and impure aldehyde (3.5 g) as an oil. A mixture of the aldehyde (3.5 g), PPTS (500 mg; 0.50 mmol) and ethylene glycol (5.0 mL; 89 mmol) in toluene (50 mL) was heated to reflux in a Dean-Stark apparatus overnight. The reaction was cooled to RT, washed with aqueous Na<sub>2</sub>CO<sub>3</sub> and brine (50 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo to give an oil. This material was chromatographed (SiO<sub>2</sub>; 3:1 hexane:EtOAc) to give Part D compound (1.35 g; 30%) as a clear oil.

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E.

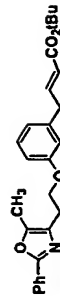


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A solution of Part D compound (1.35 g; 3.7 mmol), glacial acetic acid (10 mL) and H<sub>2</sub>O (2 mL) was heated at 80°C for 48 h. H<sub>2</sub>O (100 mL) was added and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with H<sub>2</sub>O (2 x 100 mL), saturated aqueous NaHCO<sub>3</sub> (2 x 100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo to give Part E compound (1.24 g; 99%) as a brown oil.

20

F.



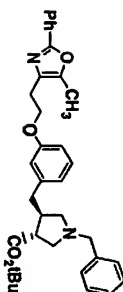
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A mixture of Part E compound (500 mg; 1.55 mmol) and tert-butyl (triphenylphosphoranylidene) acetate (600 mg; 1.59 mmol) in toluene (100 mL) was heated to reflux for 1 h. Analytical HPLC showed that the reaction was complete. After cooling, volatiles were removed in vacuo and the residue was chromatographed (SiO<sub>2</sub>; hex:EtOAc 3:1) to give Part F compound (390 mg; 60%) as an oil.

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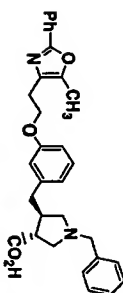
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G.



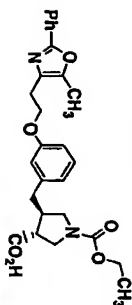
- 5 A mixture of Part E compound (100 mg; 0.238 mmol), Part B compound (85 mg; 0.36 mmol) and a catalytic amount of TFA (1  $\mu$ L) in toluene (1.0 mL) was stirred at RT for 3 h. TLC showed that the reaction was complete at this point. Volatiles were removed in vacuo and the residue was chromatographed (SiO<sub>2</sub>; hex:EtOAc 1:1) to provide Part G compound (110 mg; 93%) as an oil.

H.

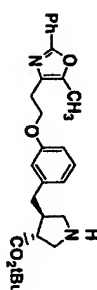


- 15 A solution of Part G compound (22 mg; 0.036 mmol) and TFA (1 mL) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was stirred at RT for 6 h. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; flow rate = 20 mL/min; 10 min continuous gradient from 30:70 B:A to 100% B + 5 min hold-time at 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give the racemic title compound (17 mg; 97%). [M + H]<sup>+</sup> = 497.2

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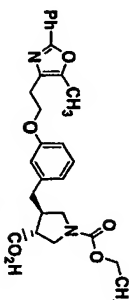
Example 2

A.



- 5 A mixture of Example 1 Part G compound (94 mg; 0.19 mmol) and 10% Pd/C (10 mg) in MeOH (10 mL) under an atmosphere of H<sub>2</sub> was stirred at RT for 3 h. At this point analytical HPLC showed that the reaction was complete. The catalyst was filtered off on a pad of Celite<sup>®</sup> and the filtrate was concentrated in vacuo to give crude Part A compound which was used in the next reaction without further purification.

B.

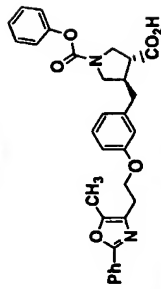


- 15 To a 0°C solution of crude Part A compound (10 mg; 0.022 mmol) and DMAP (150 mg; 1.23 mmol) in pyridine (1 mL) was added dropwise ethyl chloroformate (500  $\mu$ L; 5.23 mmol). The reaction mixture was stirred at 60°C for 2 h. At this point TLC indicated that all starting material had been consumed. Volatiles were removed in vacuo; the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and TFA (1.5 mL) and the reaction was stirred at RT for 1 h. Volatiles were removed in vacuo and the residue was partitioned between EtOAc (5 mL) and H<sub>2</sub>O (3 mL). The organic phase was washed with H<sub>2</sub>O (2 x 3 mL) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1) to furnish the title compound (5.6 mg; 53%).

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$[M + H]^+ = 479.3$

### Example 3

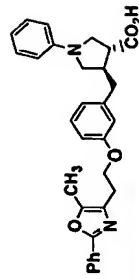


5 Example 3 (6.6 mg; 57%) was synthesized employing the procedure described in Example 2, except that phenyl chloroformate was used in the sequence instead of ethyl chloroformate.

$[M + H]^+ = 527.2$

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### Example 4



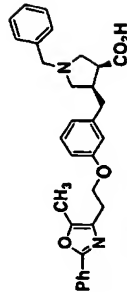
15 A mixture of Example 2 Part A compound (20 mg; 0.043 mmol), bromobenzene (10 mg; 0.263 mmol), 1,3-bis(diphenylphosphino)propane (DPPP; 2 mg;  $4.8 \times 10^{-3}$  mmol), sodium tert-butoxide (2 mg; 0.018 mmol) and  $Pd_2(dibenzylacetone)_3$  (1 mg;  $1 \times 10^{-3}$  mmol) in toluene (2 mL) was stirred at 90°C for 6 h. At this point HPLC showed that all starting material had been consumed. The reaction mixture was cooled to RT and partitioned between EtOAc (10 mL) and aqueous 1 N HCl (10 mL). The organic phase was washed with  $H_2O$  (2 x 20 mL), dried ( $Na_2SO_4$ ), and concentrated in vacuo. The residue was dissolved in TFA: $CH_2Cl_2$  (1 mL of a 1:1 solution) and the reaction was stirred at RT for 1 h. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (as

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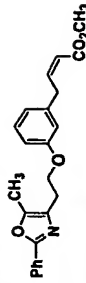
described for Example 1) to provide the title compound (7 mg; 48%) as an oil.  
 $[M + H]^+ = 483.2$

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### Example 5



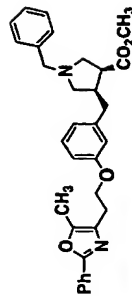
A.



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To a -78°C solution of  $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$  (1.47 g; 4.62 mmol) and 18-crown-6 (6.10 g; 23 mmol) in anhydrous THF (50 mL) under  $N_2$  was added dropwise 15 potassium hexamethyldisilazide (9.2 mL of a 0.5M solution in toluene; 4.62 mmol). The solution was stirred at -78°C for 30 min, after which a solution of the aldehyde (Example 1 Part E compound; 1.24 g; 3.86 mmol) in THF (50 mL) was added dropwise. The reaction mixture was stirred 20 for 30 min at -78°C, after which excess saturated aqueous  $NH_4Cl$  (50 mL) was added. The mixture was allowed to warm to RT and extracted with  $Et_2O$  (3 x 30 mL). The combined organic extracts were dried ( $Na_2SO_4$ ), concentrated in vacuo, and the residue was chromatographed ( $SiO_2$ ; 3:1 25 hexane:EtOAc) to give Part A compound (343 mg; 23%) as an oil.

B.

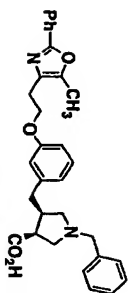


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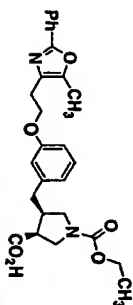
A mixture of Part A compound (343 mg; 0.908 mmol), Example 1 Part B compound (300 mg; 1.26 mmol) and a catalytic amount of TFA (5  $\mu$ L) in toluene (5.0 mL) was stirred at RT for 3 h. TLC showed that the reaction was complete at this point. Volatiles were removed in vacuo and the residue was chromatographed (SiO<sub>2</sub>; hex:EtOAc 1:1) to provide Part B compound (450 mg; 98%) as an oil.

C.



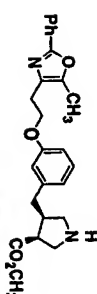
A solution of Part B compound (27 mg; 0.053 mmol), aqueous LiOH (1 mL of a 1 M solution) and THF (2 mL) was stirred at RT for 5 h. At this point, LC/MS indicated that the reaction was complete. The mixture was acidified with aqueous HCl (5 mL of a 1 M solution) and extracted with EtOAc (10 mL). The organic phase was washed with H<sub>2</sub>O (2 x 5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1) to give the title compound (24 mg; 91%) as a white lyophilate. [M + H]<sup>+</sup> = 497.3

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Example 6

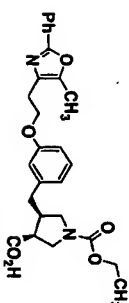
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A.



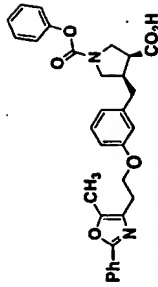
A mixture of Example 5 Part B compound (580 mg; 1.17 mmol) and 10% Pd/C (50 mg) in MeOH (25 mL) under an atmosphere of H<sub>2</sub> was stirred at RT for 18 h. At this point analytical HPLC showed that the reaction was complete. The catalyst was filtered off (using a pad of Celite®) and the filtrate was concentrated in vacuo to give crude Part A compound (400 mg; 81%) as an oil which was used in the next reaction without further purification.

B.



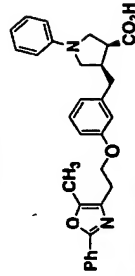
To a 0°C solution of crude Part A compound (10 mg; 0.022 mmol) and DMAP (150 mg; 1.23 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added dropwise ethyl chloroformate (500  $\mu$ L; 5.23 mmol). The reaction mixture was then stirred at RT for 5 h. At this point TLC indicated that all starting material had been consumed. Volatiles were removed in vacuo and the residue was dissolved in a solution of THF (1 mL) and aqueous LiOH (1 mL of a 1 M solution) and the reaction was stirred at RT for 12 h. The reaction mixture was acidified with aqueous HCl (2 mL of a 1 M solution) and extracted with EtOAc (10 mL). The organic phase was washed with H<sub>2</sub>O (2 x 5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1) to give the title compound (6.0 mg; 56%) as a white lyophilate. [M + H]<sup>+</sup> = 479.3



Example 7

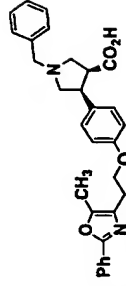
Example 7 compound (6.2 mg; 53%) was synthesized employing the procedure described in Example 6, except that phenyl chloroformate was used in the sequence instead of ethyl chloroformate.

$[M + H]^+ = 479.3$

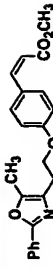
Example 8

A mixture of Example 6 Part A compound (30 mg; 0.071 mmol), phenylboronic acid (15 mg; 0.123 mmol),  $\text{Cu}(\text{OAc})_2$  (4 mg; 0.022 mmol), myristic acid (3 mg; 0.013 mmol) and 2,6 lutidine (10  $\mu\text{L}$ ; 0.056 mmol) in toluene (2 mL) was stirred at RT for 24 h in air. At this point HPLC showed that product had been formed. The reaction mixture was eluted through an  $\text{SiO}_2$  cartridge with 1:1 hexane:EtOAc. The combined eluent fractions were concentrated in vacuo and the residue was taken up in aqueous LiOH (0.5 mL of a 1 M solution) and THF (1 mL). The reaction was stirred at RT for 2 h; TLC indicated that the reaction was complete at this point. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (as described for Example 1) to provide the title compound (6 mg; 17%) as an oil.

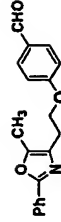
$[M + H]^+ = 483.2$

Example 9

5 A.

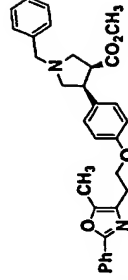


To a  $-78^\circ\text{C}$  solution of  $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{CH}_3$  (372 mg; 1.17 mmol) and 18-crown-6 (1.55 g; 5.85 mmol) in anhydrous THF (5 mL) under  $\text{N}_2$  was added dropwise potassium hexamethyldisilazide (2.34 mL of a 0.5 M solution in toluene; 1.17 mmol). The solution was stirred at  $-78^\circ\text{C}$  for 30 min, after which a solution of the aldehyde Example 47 Part B compound (300 mg; 0.977 mmol)



20 in THF (5.5 mL) was added dropwise. The reaction mixture was stirred for 30 min at  $-78^\circ\text{C}$ , after which excess saturated aqueous  $\text{NH}_4\text{Cl}$  (50 mL) was added. The mixture was allowed to warm to RT and extracted with  $\text{Et}_2\text{O}$  (3 x 30 mL). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), concentrated in vacuo, and the residue was chromatographed ( $\text{SiO}_2$ ; 3:1 hexane:EtOAc) to give Part A compound (317 mg; 89%) as an oil.

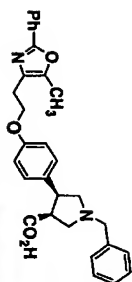
B.



30

A mixture of Part A compound (31.7 mg; 0.87 mmol), Example 1 Part B compound (300 mg; 1.26 mmol) and a catalytic amount of TFA (5  $\mu$ L) in toluene (5.0 mL) was stirred at RT for 3 h. TLC showed that the reaction was complete at this point. Volatiles were removed in vacuo and the residue was chromatographed (SiO<sub>2</sub>; hex:EtOAc 1:1) to provide Part B compound (400 mg; 92%) as an oil.

10 C.

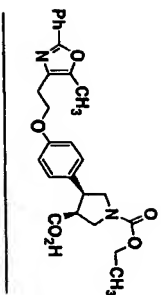


A solution of Part B compound (13 mg; 0.026 mmol) in aqueous LiOH (0.5 mL of a 1 M solution) and THF (1 mL) was stirred at RT for 2 h; TLC indicated that the reaction was complete at this point. The reaction mixture was acidified with aqueous HCl (2 mL of a 1 M solution) and extracted with EtOAc (10 mL). The organic phase was washed with H<sub>2</sub>O (2 x 5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1) to provide the title compound (6 mg; 48%) as an oil.

$$[M + H]^+ = 483.2$$

25

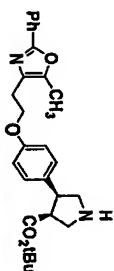
### Example 10



A.

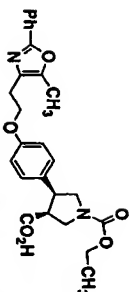
**WO 2004/004665**

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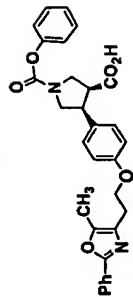
5 A mixture of Example 9 Part B compound (400 mg; 0.805 mmol) and 10% Pd/C (50 mg) in MeOH (15 mL) under an atmosphere of H<sub>2</sub> was stirred at RT for 5 h. At this point analytical HPLC showed that the reaction was complete. The catalyst was filtered off (using a pad of Celite®) and the filtrate was concentrated in vacuo to give crude Part A compound (280 mg; 85%) as an oil which was used in the next reaction without further purification.

15 B.



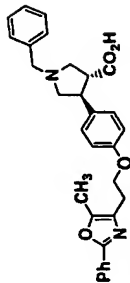
To a 0°C solution of crude Part A compound (15 mg, 0.037 mmol) and DMAP (13 mg, 0.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was added dropwise ethyl chloroformate (7  $\mu\text{L}$ ; 0.06 mmol). The reaction mixture was then stirred at RT for 3 h. At this point HPLC indicated that all starting material had been consumed. TFA in  $\text{CH}_2\text{Cl}_2$  was added (1 mL of a 1:1 solution) and the reaction was stirred at RT for 1 h. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (as described for Example 1) to give the title compound (6.4 mg, 36%) as an oil.

$[\text{M} + \text{H}]^+ = 465.3$

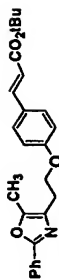
Example 11

5 The racemic title compound (2.7 mg; 14%) was prepared employing the procedure described in Example 10, except that phenyl chloroformate (8  $\mu$ L; 0.06 mmol) was used in the sequence instead of ethyl chloroformate.

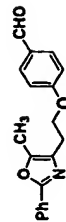
10  $[M + H]^+ = 513.4$

Example 13

A.



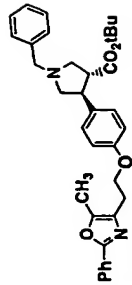
20 A mixture of  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{tBu}$  (200 mg; 0.53 mmol) and the aldehyde Example 47 Part B compound (150 mg; 0.49 mmol)



25 in toluene (20 mL) was heated at 100°C for 2 h. At this point LC/MS indicated that all starting aldehyde had been consumed. The reaction mixture was cooled to RT and 30 volatiles were removed in vacuo. The residue was

chromatographed ( $\text{SiO}_2$ ; 3:1 hexane:EtOAc) to provide Part A compound (120 mg; 60%) as a clear oil.

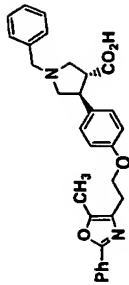
B.



A mixture of Part A compound (120 mg; 0.30 mmol), Example 1 Part B compound (100 mg; 0.421 mmol) and a catalytic amount of TFA (5  $\mu$ L) in  $\text{CH}_2\text{Cl}_2$  (5.0 mL) was stirred at RT for 24 h. HPLC showed that the reaction was complete at this point. Volatiles were removed in vacuo and the residue was chromatographed ( $\text{SiO}_2$ ; hex:EtOAc 3:1) to provide Part B compound (143 mg; 88%) as an oil.

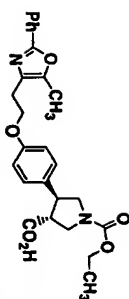
15

C.

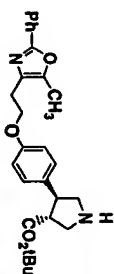


20 A solution of Part B compound (20 mg; 0.037 mmol) in aqueous LiOH (0.5 mL of a 1 M solution) and THF (1 mL) was stirred at RT for 2 h; TLC indicated that the reaction was complete at this point. The reaction mixture was acidified with aqueous HCl (2 mL of a 1 M solution) and extracted with EtOAc (10 mL). The organic phase was washed with  $\text{H}_2\text{O}$  (2 x 5 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1) to provide 30 the title compound (6 mg; 33%) as an oil.

$[M + H]^+ = 483.2$

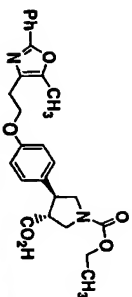
Example 14

5 A.



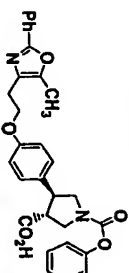
A mixture of Example 10 Part B compound (143 mg; 0.265 mmol) and 10% Pd/C (30 mg) in MeOH (10 mL) under an atmosphere of H<sub>2</sub> was stirred at RT for 3 h. At this point analytical HPLC showed that the reaction was complete. The catalyst was filtered off (using a pad of Celite®) and the filtrate was concentrated in vacuo to give crude Part A compound (82 mg; 69%) as an oil which was used in the next reaction without further purification.

B.

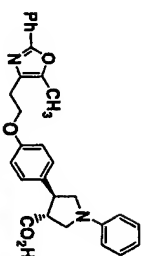


To a 0°C solution of crude Part A compound (15 mg; 0.033 mmol) and DMAP (15 mg; 0.122 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added dropwise ethyl chloroformate (7 µL; 0.06 mmol). The reaction mixture was then stirred at RT for 3 h. At this point HPLC indicated that all starting material had been consumed. TFA in CH<sub>2</sub>Cl<sub>2</sub> was added (1 mL of a 1:1 solution) and the reaction was stirred at RT for 1 h.

Volatiles were removed in vacuo and the residue was purified by preparative HPLC (as described for Example 1) to give the title compound (16 mg; 57%) as an oil.  
[M + H]<sup>+</sup> = 465.3

Example 15

Example 15 compound (19 mg; 62%) was prepared employing the procedure as described in Example 11, except that phenyl chloroformate (8 µL; 0.04 mmol) was used in the sequence instead of ethyl chloroformate.  
[M + H]<sup>+</sup> = 513.4

Example 16

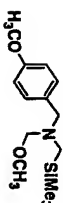
The procedure of Example 8 was essentially followed to prepare the title compound.

A mixture of Example 14 Part A compound (40 mg; 0.089 mmol), phenylboronic acid (12 mg; 0.10 mmol), Cu(OAc)<sub>2</sub> (1 mg; 5.5 x 10<sup>-3</sup> mmol), myristic acid (1 mg; 4.3 x 10<sup>-3</sup> mmol) and 2,6 lutidine (18 µL; 0.16 mmol) in toluene (1 mL) was stirred at RT for 24 h in air. At this point HPLC showed that product had been formed. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in a



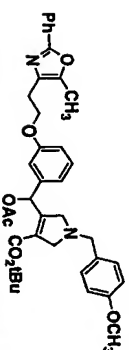
concentrated in vacuo to provide crude Part C compound (7.6 g; 41%) as an oil, which was used in the next step without further purification.

5 D.



To a 0°C solution of 37% aqueous formaldehyde (2.8 g; 34 mmol) was added dropwise crude Part C compound (7.6 g; 34 mmol) followed by 5 drops of aqueous 1 N NaOH (in order to neutralize the formic acid in the formaldehyde). The reaction mixture was stirred at 0°C for 10 min, after which MeOH (5 mL) was added in one portion. K<sub>2</sub>CO<sub>3</sub> (4 g) was added to absorb the aqueous phase, after which the mixture was stirred at RT for 1 h and then filtered. Additional K<sub>2</sub>CO<sub>3</sub> (2 g) was added to the filtrate and the mixture was stirred at RT for an additional 12 h. Et<sub>2</sub>O (20 mL) was then added and the mixture was filtered; the filtrate was concentrated in vacuo and the residual oil was distilled under reduced pressure (bp = 80°C @ 0.5 mm Hg) to give Part D compound (4.2 g; 46%) as a clear oil.

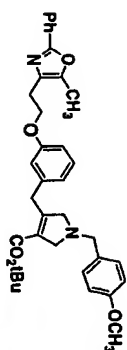
E.



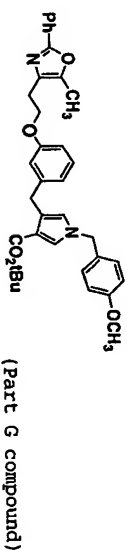
A mixture of Part B compound (130 mg; 0.273 mmol), Part D compound (73 mg; 0.273 mmol) and TFA (catalytic amount; several drops) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was stirred at RT for 2 h. At this point the reaction was complete by TLC. Volatiles were removed in vacuo and the mixture was

chromatographed (SiO<sub>2</sub>; 3:1 hexane:EtOAc) to provide Part E compound (171 mg; 98%) as an oil.

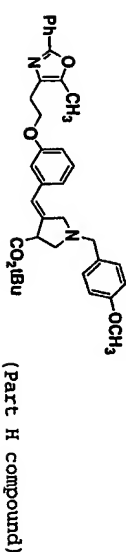
F.



A solution of Part E compound (360 mg; 0.564 mmol), (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (4 mg; 0.006 mmol) and formic acid/Et<sub>3</sub>N (0.50 mL of a 1:1 4M solution in dioxane; 1.69 mmol) in dioxane (5 mL) was refluxed N<sub>2</sub> for 30 min. At this point LC-MS indicated that all starting material had been consumed. The reaction mixture was cooled to RT, diluted with EtOAc (5 mL) and washed with H<sub>2</sub>O (2 x 10 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (ISCO chromatography apparatus; 25 g SiO<sub>2</sub> column; continuous gradient from hexane -> 70:30 hexane:EtOAc) to provide Part F compound (114 mg; 35%) in addition to the pyrrole (Part G compound; 80 mg; 25%)

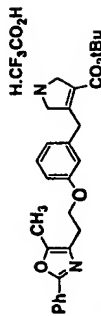


as well as the pyrrolidine (Part H compound; 25 mg; 8%)



as byproducts.

I.



5

To a -78°C solution of Part F compound (114 mg;

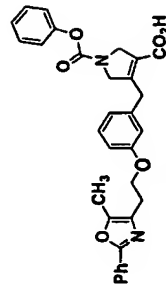
0.1969 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was added  $\text{CH}_2\text{CHClOCCl}$  (45  $\mu\text{L}$ ; 0.40 mmol). The reaction mixture was stirred at -78°C for 30 min, then was allowed to warm to RT and stirred at RT for 1 h. At this point, HPLC indicated that all starting material had been consumed. Volatiles were removed in vacuo and MeOH (5 mL) was added; the solution was then stirred at RT for 8 h. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (YMC reverse-phase ODS 30 x 250 mm column; flow rate = 25 mL/min; 30 min continuous gradient from 30:70 B:A to 100% B + 10 min hold-time at 100% B, where solvent A = 90:10:0.1  $\text{H}_2\text{O}$ :MeOH:TFA and solvent B = 90:10:0.1 MeOH: $\text{H}_2\text{O}$ :TFA) to provide Part I compound (81 mg; 89%) as a TFA salt.

10

A solution of Example 17 Part J compound (25 mg; 0.054 mmol), ethyl chloroformate (11 mg; 0.10 mmol) and DMAP (61 mg; 0.50 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was stirred at RT for 30 min. EtOAc (10 mL) was then added and the mixture was successively washed with  $\text{H}_2\text{O}$  (2 x 20 mL) and aqueous 1 N HCl (10 mL), then dried ( $\text{Na}_2\text{SO}_4$ ). Volatiles were removed in vacuo and the residual oil was dissolved in TFA/ $\text{CH}_2\text{Cl}_2$  (1 mL of a 1:1 mixture) and the reaction was stirred at RT for 1 h, after which volatiles were removed in vacuo. The residue was purified by preparative HPLC (using the same conditions as described for Example 1) to provide Example 16 compound (17 mg; 66%) as an oil.

15

J.



25

A solution of Part I compound (18 mg; 0.032 mmol), phenyl chloroformate (6.3  $\mu\text{L}$ ; 0.05 mmol) and DMAP (11 mg; 0.09 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was stirred at RT for 30 min. EtOAc (10 mL) was then added and the mixture was successively washed with  $\text{H}_2\text{O}$  (2 x 20 mL) and aqueous 1 N HCl (10 mL), then dried ( $\text{Na}_2\text{SO}_4$ ). Volatiles were removed

30

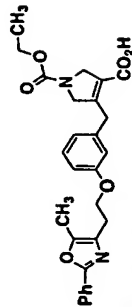
in vacuo and the residual oil was dissolved in TFA/ $\text{CH}_2\text{Cl}_2$  (1 mL of a 1:1 mixture) and the reaction was stirred at RT for 1 h, after which volatiles were removed in vacuo. The residue was purified by preparative HPLC (as described for Example 1) to provide the title compound (13 mg; 78%) as an oil.

5

[M + H]<sup>+</sup> = 525.1

# Example 18

10



15

A solution of Example 17 Part J compound (25 mg; 0.054 mmol), ethyl chloroformate (11 mg; 0.10 mmol) and DMAP (61 mg; 0.50 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was stirred at RT for 30 min. EtOAc (10 mL) was then added and the mixture was successively washed with  $\text{H}_2\text{O}$  (2 x 20 mL) and aqueous 1 N HCl (10 mL), then dried ( $\text{Na}_2\text{SO}_4$ ). Volatiles were removed in vacuo and the residual oil was dissolved in TFA/ $\text{CH}_2\text{Cl}_2$  (1 mL of a 1:1 mixture) and the reaction was stirred at RT for 1 h, after which volatiles were removed in vacuo. The residue was purified by preparative HPLC (using the same conditions as described for Example 1) to provide Example 16 compound (17 mg; 66%) as an oil.

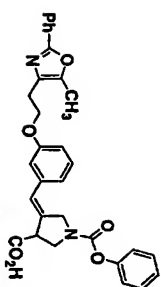
20

25

[M + H]<sup>+</sup> = 477.1

# Example 19

30



Example 19 compound was prepared from Example 17

Part G compound (16 mg; 0.035 mmol) with phenyl

5 chloroformate (13  $\mu$ L; 0.10 mmol) using the 2-step

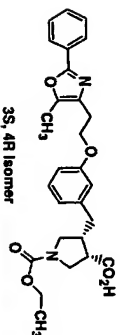
sequence as employed in the synthesis of Example 17 from Example 17 Part J compound. Example 19 compound was

obtained (9 mg; 49%) as a white solid after preparative HPLC (using the same conditions as described in Example

1).

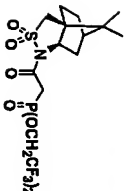
$[M + H]^+ = 525.1$

#### Example 19A



3S, 4R isomer

A.



20

To a RT solution of D-(1S)-(-)-2,10-camphorsultam (1.0 g; 4.64 mmol) in anhydrous toluene (5 mL) under an atmosphere of argon was added MeAl (2.3 mL of a 2.0 M solution in toluene; 4.6 mmol). The solution was stirred at RT for 1 h, after which  $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$  (1.50 g; 4.71 mmol) was added. The reaction was stirred at 75°C for 3 days, cooled to RT, and partitioned between

saturated aqueous  $NH_4Cl$  (50 mL) and  $Et_2O$  (25 mL). The organic phase was dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ;

hexane:EtOAc 3:1) and further purified by preparative

5 HPLC (YMC ODS reverse phase 30 x 250 mm column; flow rate = 25 mL/min; 30 min continuous gradient from 80:20 A:B to

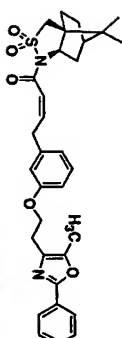
100% B; where A = 90:10:0.1  $H_2O$ :MeOH:TFA; B = 90:10:0.1

MeOH: $H_2O$ :TFA, then 15 min hold at 100% B) to give Part A

compound (491 mg; 21%) as an oil.

10

B.



15

To a -78°C solution of Part A compound (491 mg; 0.98 mmol) and 18-crown-6 (2.1 g; 8 mmol) in THF (20 mL) under an atmosphere of  $N_2$  was added dropwise a solution of  $KN(TMS)_2$  (2.35 mL of a 0.5 M solution in toluene; 1.18 mmol). The reaction was stirred at -78°C for 30 min,

20

after which a solution of the aldehyde (Example 1 Part E compound; 377 mg; 1.18 mmol) in THF (5 mL) was added and

the reaction was stirred at -78°C for a further 30 min.

Saturated aqueous  $NH_4Cl$  (5 mL) was then added slowly and the reaction was allowed to warm to RT. The mixture was

25

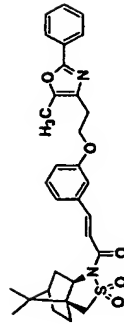
extracted with  $Et_2O$  (3 x 30 mL), dried ( $Na_2SO_4$ ) and concentrated in vacuo. The crude product was

chromatographed ( $SiO_2$ ; hexane:EtOAc 3:1) to provide Part

B compound (Z-isomer; 100 mg; 18%) as an oil. In

addition the isomeric Part C compound



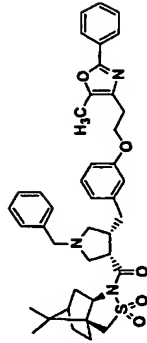


(Part C compound)

(E-isomer; 50 mg; 9%) was also obtained.

5

C.

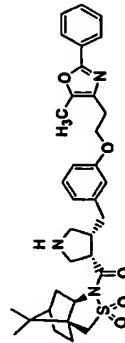


A mixture of Part B compound (100 mg; 0.178 mmol),

Example 1 Part B compound (100 mg; 0.421 mmol) and a catalytic amount of TFA (5  $\mu$ L) in toluene (2.0 mL) was stirred at RT for 3 h. TLC showed that the reaction was complete. The reaction mixture was partitioned between EtOAc (10 mL) and saturated aqueous NaHCO<sub>3</sub> (20 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; hex:EtOAc 3:1) to provide Part C compound (56 mg; 45%) as an oil.

15

D.

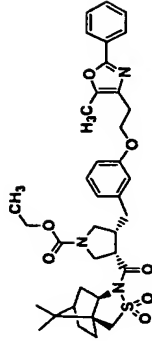


20

A mixture of Part C compound (56 mg; 0.081 mmol) and 10% Pd/C (30 mg) in MeOH (5 mL + 1 drop of HOAc) was stirred under an atmosphere of H<sub>2</sub> at RT for 5 h. The mixture was filtered, and the filtrate was concentrated in vacuo to give Part D compound (42 mg; 85%) as an oil.

25

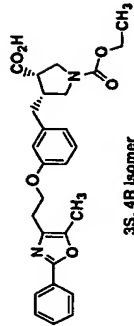
E.



A mixture of Part D compound (20 mg; 0.033 mmol), DMAP (12 mg; 0.1 mmol) and ethyl chloroformate (5 mg; 0.05 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at RT for 30 min, then was partitioned between EtOAc (10 mL) and H<sub>2</sub>O (20 mL). The organic phase was washed with H<sub>2</sub>O and aqueous 1 M HCl (10 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hexane to 30:70 hexane:EtOAc over 25 min) to give Part E compound (4 mg; 18%) as an oil.

5

F.



15

A solution of Part E compound (4 mg; 5.9 x 10<sup>-3</sup> mmol) in aqueous LiOH (1 mL of a 1 N solution) and THF (2 mL) was stirred at RT for 3 h, then was partitioned between excess aqueous 1 M HCl and EtOAc. The organic phase was washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for the synthesis of Example 1) to give the title compound (0.9 mg; 32%).

25

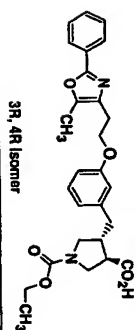
[M + H]<sup>+</sup> = 479.2

Chiral analytical HPLC (Daicel Chiralcel OJ-H 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 80:20 A:B, where A = heptane + 0.1% TFA and B = 50:50:0.1 MeOH:EtOH:TFA; detector wavelength = 220 nm; retention time = 20.0 min; ee = 95%

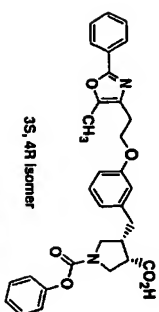
30

The rest of the material was the chiral epimerized trans isomer:

Example 19B compound



Example 20

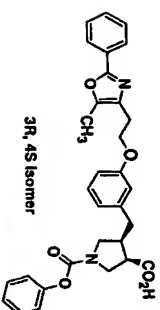


Example 20 compound (0.5 mg; 16%) was prepared

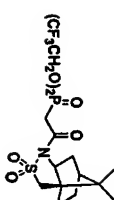
from Example 19A Part D compound (using the same sequence as the synthesis of Example 19A from Example 19A Part D compound). [M + H]<sup>+</sup> = 527.2

Chiral analytical HPLC (Daicel Chiralcel OD 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 85:15 A:B, where A = heptane + 0.1% TFA; B = 50:50:0.1 MeOH:EtOH:TFA; detector wavelength = 220 nm; retention time = 21.3 min; ee = 93%

Example 21

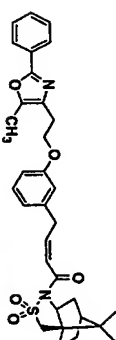


A.



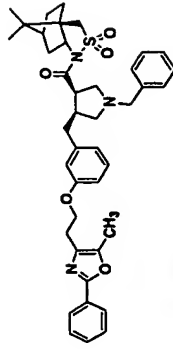
Part A compound (630 mg; 27%) was synthesized in exactly the same way as Example 19 Part A compound except that L-(1S)-(-)-2,10-camphorsultam (1.0 g) was used in place of D-(1R)-(+)-2,10-camphorsultam.

B.

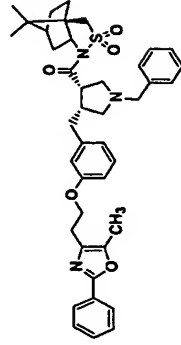


To a -78°C solution of Part A compound (630 mg; 1.26 mmol) and 18-crown-6 (2.66 g; 10.1 mmol) in anhydrous THF (25 mL) under N<sub>2</sub> was added dropwise a solution of KN(TMS)<sub>2</sub> (2.51 mL of a 0.5 M solution in toluene; 1.26 mmol). The reaction was stirred at -78°C for 15 min, after which a solution of Example 1 Part B compound (610 mg; 1.90 mmol) in THF (5 mL) was added dropwise. The reaction was stirred at -78°C for a further 30 min, then quenched by cautious addition of excess H<sub>2</sub>O. The reaction was allowed to warm to RT and partitioned between saturated aqueous NH<sub>4</sub>Cl and EtOAc. The organic phase was washed with H<sub>2</sub>O and brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hexane to 100% EtOAc over 50 min) to provide the Z-olefin Part B compound (293 mg; 28%) as an oil. In addition, the corresponding E-olefin Part C compound (149 mg; 14%) was also obtained.

D.

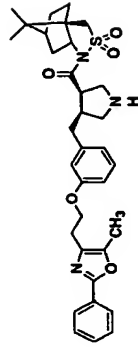


To a solution of Part B compound (290 mg; 0.517 mmol) in toluene (1.3 mL) were successively added Example 1 Part B compound (270 mg; 1.14 mmol) and a catalytic amount of TFA (1  $\mu$ L). The reaction was stirred at RT for 3 h, then was partitioned between EtOAc and saturated aqueous NaHCO<sub>3</sub>. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hexane to 100% EtOAc over 40 min) to provide Part D compound (176 mg; 49%) as well as a diastereomeric product (41 mg; 11%), which corresponds to Example 19 Part C compound.



(Ex. 19 Part C compound)

E.

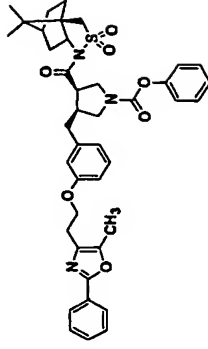


A mixture of Part D compound (87 mg; 0.126 mmol) and 10% Pd/C (42 mg) in MeOH:EtOAc (2.5 mL of a 4:1 solution) was stirred under an atmosphere of H<sub>2</sub> at RT for 24 h.

20

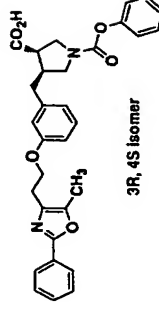
The mixture was filtered and the filtrate was concentrated in vacuo to give Part E compound (70 mg; 92%) as an oil.

5 F.



A mixture of Part E compound (35 mg; 0.058 mmol), Et<sub>3</sub>N (16  $\mu$ L; 0.12 mmol), DMAP (one crystal) and phenyl chloroformate (15  $\mu$ L; 0.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at RT for 2 h, then was partitioned between aqueous 1 N HCl and EtOAc. The organic phase was washed with H<sub>2</sub>O and brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hexane to 100% EtOAc over 35 min) to give Part F compound (30 mg; 72%) as an oil.

G.



3R, 4S isomer

A mixture of Part F compound (15 mg; 0.021 mmol) and LiOH.H<sub>2</sub>O (40 mg; 0.95 mmol) in THF/H<sub>2</sub>O (4 mL of a 2:1 solution) was stirred at RT for 18 h. EtOAc was added and the reaction acidified to pH ~ 2 with aqueous 1 N HCl. The organic phase was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from 1:1

20

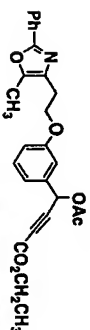
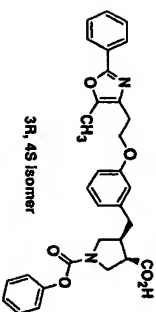
25

hex:EtOAc to 10:10:1 hex:EtOAc:acetic acid) to give the title compound (6.5 mg; 60%) as a white solid.

$[M + H]^+ = 527.6$

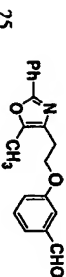
Chiral analytical HPLC (Daicel Chiralcel OD 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 85:15 A:B, where A = heptane + 0.1% TFA; B = 50:50:0.1 MeOH:EtOH:TFA; detector wavelength = 220 nm; retention time = 15.6 min; ee = 99%

#### Example 21 (Alternative Synthesis)



A.

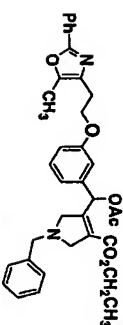
To a RT solution of ethyl trimethylsilylpropionate (2.65 g; 15.6 mmol) and aldehyde Example 436 Part A compound (4.0 g; 13.0 mmol)



in  $\text{CH}_2\text{Cl}_2$  (100 mL) were successively added potassium fluoride (910 mg; 15.6 mmol) and 18-crown-6 (1.26 g; 4.7 mmol). The reaction mixture was stirred at RT for 18 h, after which a solution of concentrated HCl (5 mL) in MeOH (20 mL) was added slowly. The solution was stirred for 3

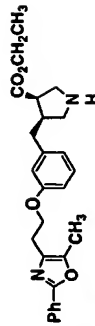
h at RT, then washed with aqueous 1 N HCl and brine. The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (40 mL) and acetyl chloride (1.20 g; 15.6 mmol) and  $\text{Et}_3\text{N}$  (2.2 mL; 15.6 mmol) were successively added slowly to this solution. The reaction was stirred at RT for 30 min, then washed with brine and saturated aqueous  $\text{NaHCO}_3$ . The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The crude product was chromatographed ( $\text{SiO}_2$ ; heptane:EtOAc 7:3) to give Part A compound (3.26 g; 56%) as a pale yellow oil.

B.

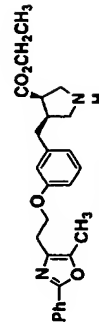


To a RT solution of Part A compound (2.50 g; 5.60 mmol) in  $\text{CH}_2\text{Cl}_2$  (40 mL) was added a solution of Example 1 Part B compound (1.70 g; 7.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (40 mL). The solution was stirred at RT for 10 min, after which TFA (0.50 mL) was added dropwise. The reaction was stirred at RT for 1 h, after which HPLC indicated that 30% of Part A compound still remained. Additional Example 1 Part A compound (0.57 g; 2.4 mmol) was added and the reaction was stirred for 30 min longer. The solution was washed with saturated aqueous  $\text{NaHCO}_3$ , dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; heptane:EtOAc 6:4) to give crude Part B compound (2.3 g) as a pale yellow oil.

C.



A mixture of crude Part B compound (2.3 g), 10% Pd/C (5 (600 mg) and concentrated HCl (5 drops) in MeOH (40 mL) was stirred under an atmosphere of H<sub>2</sub> (60 psi) for 96 h. The catalyst was filtered off (Celite®) and the filtrate was concentrated in vacuo; the residue was partitioned between EtOAc and aqueous 1 N NaOH. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>:MeOH 10:1) to give racemic Part C compound (1.70 mg; 70% for 2 steps) as a pale yellow oil. The individual enantiomers were separated at this point by preparative HPLC under the following conditions: Chiralcel OD chiral column, 5 cm x 50 cm; 20 µM; Flow rate = 45 mL/min; isocratic solvent system = 80% heptane + 0.1% Et<sub>2</sub>NH & 20% IPA + 0.1% Et<sub>2</sub>NH. Part C compound (1.72 g) was chromatographed in 3 runs. The first fraction elutes under these conditions @ 45 min-1 hour and was subsequently determined to be the (3R, 4S) enantiomer (see below) (Part D compound).

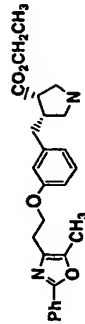


3R, 4S enantiomer (Part D compound)

25

The second fraction elutes under these conditions @ 1 hour-1 hour 15 min. This fraction was subsequently determined to be the (3S, 4R) enantiomer (see below) (Part E compound).

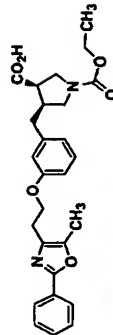
30



3S, 4R enantiomer (Part E compound)

5

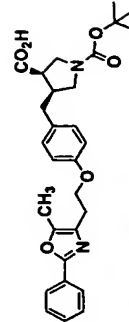
## Example 22



The title compound (4.3 mg; 16% for 2 steps) was prepared from Example 21 Part E compound using the same 2-step sequence as for the synthesis of Example 21. [M + H]<sup>+</sup> = 479.5

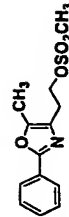
Chiral analytical HPLC (Daicel Chiralcel OD 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 80:20 A:B, where A = heptane + 0.1% TFA; B = 50:50:0.1 MeOH:EtOH:TFA; detector wavelength = 220 nm; retention time = 14.6 min; ee = 99%

## Example 23



A.

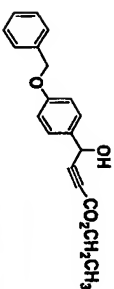
25



To a -5°C solution of 5-phenyl-2-methyl-oxazole-4-ethanol (20.00 g, 0.098 mol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added

methanesulfonyl chloride (12.40 g, 0.108 mol) in one portion (exothermic reaction). After recooling to -5°C, Et<sub>3</sub>N (11.1 g, 0.110 mol) was added slowly over 30 min (internal temperature <3°C). The reaction was allowed to warm to RT and stirred for 1 h (reaction monitored by analytical HPLC), at which point starting material had been consumed. The reaction was washed with aqueous HCl (2 x 50 mL of a 3N solution). The combined aqueous layers were extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The combined organic extracts were successively washed with satd. aqueous NaHCO<sub>3</sub> and brine (50 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to ~30 mL volume. Methyl tert-butyl ether (120 mL) was added and the mixture was stirred; a white solid was formed. The mixture was cooled to -20°C for complete crystallization. The product was filtered and vacuum-dried to give Part A compound (23.3 g, 85%) as a white solid. The mother liquor was concentrated in vacuo and recrystallized from methyl tert butyl ether/heptane to give a second crop of Part A compound (3.3 g, 12%); total yield = 97%.

B.

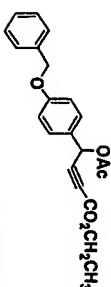


To a -78°C solution of ethyl propynoate (10.0 g; 100 mmol) in anhydrous THF (200 mL) was added dropwise n-BuLi (40 mL of a 2.5 M solution in hexane; 100 mmol) over 30 min. The reaction was stirred at -78°C for 30 min, after which a solution of 4-benzoyloxybenzaldehyde (21.0 g; 100 mmol) in THF (100 mL) was added dropwise. The reaction was stirred at -78°C for 1 h, excess saturated aqueous NH<sub>4</sub>Cl was cautiously added to quench the reaction, and the mixture was allowed to warm to RT. Volatiles were removed in vacuo and the residue was partitioned between

EtOAc and saturated aqueous NH<sub>4</sub>Cl. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc over 50 min) to give Part B compound (7.0 g; 23%) as an oil.

[M + H]<sup>+</sup> = 311; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.35 (m, 7H), 6.95 (d, J = 8.4 Hz, 2H), 5.47 (d, J = 6 Hz, 1H), 5.05 (s, 2H), 4.20 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 159.6, 137.4, 131.6, 129.0, 128.6, 128.4, 127.8, 115.6, 87.3, 78.2, 70.5, 64.3, 62.6, 14.4.

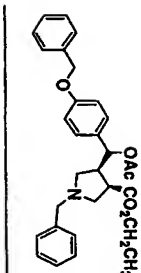
C.



To a 0°C solution of Part B compound (4.50 g; 14.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) were successively added pyridine (1.80 mL; 22.3 mmol) and acetyl chloride (1.30 mL; 18.1 mmol). The reaction was stirred at 0°C for 2 h, then was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 5% aqueous HCl. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part C compound (5.0 g; 95%) as an oil.

[M + H]<sup>+</sup> = 353; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.40 (m, 7H), 6.98 (d, 2H), 6.47 (s, 1H), 5.07 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 2.08 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 169.8, 160.1, 153.4, 137.0, 129.8, 129.0, 128.5, 128.0, 127.8, 115.6, 83.4, 78.5, 70.5, 64.9, 62.6, 21.2, 14.5.

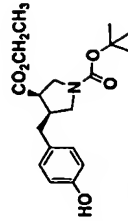
D.



To a RT solution of Part C compound (1.0 g; 2.84 mmol) in toluene (2 mL) were successively added Example 1 Part B compound (900 mg; 3.8 mmol) and TFA (100  $\mu$ L); a highly exothermic reaction occurred. The reaction was stirred at RT for 2 h, then was concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc over 50 min) to give Part D compound (700 mg; 72%) as a light yellow oil.

[M + H]<sup>+</sup> = 486; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.32 (m, 12 H), 6.88 (d, J = 8.4 Hz, 2 H), 4.98 (s, 2 H), 4.15 (q, J = 7.2 Hz, 2 H), 3.66 (m, 6 H), 2.01 (s, 3 H), 1.19 (t, 3 H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  169.5, 163.3, 158.6, 150.8, 138.8, 136.8, 130.4, 128.5, 128.5, 128.4, 127.9, 127.8, 127.4, 127.1, 114.8, 70.8, 70.0, 60.5, 60.3, 60.0, 21.0, 14.2.

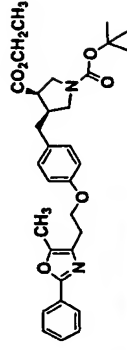
E.



A mixture of Part D compound (700 mg; 1.44 mmol) and 10% Pd/C (100 mg) in HOAc (5 mL) and TFA (1 mL) was stirred under an atmosphere of H<sub>2</sub> (balloon) for 48 h. The catalyst was filtered off on Celite<sup>®</sup> and the filtrate was concentrated in vacuo. The crude product was dissolved in THF (20 mL) and saturated aqueous NaHCO<sub>3</sub> (pH = 9); di-tert butyl dicarbonate (320 mg; 145 mmol) was added. The reaction was stirred at RT for 2 h, then was concentrated in vacuo; the residue was partitioned between EtOAc and saturated aqueous NaHCO<sub>3</sub>. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc over 50 min) to give Part E compound (300 mg; 60%) as an oil.

35

F.

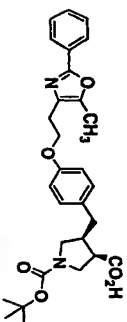


A mixture of Part E compound (50 mg; 0.14 mmol), Part A compound (50 mg; 0.17 mmol) and K<sub>2</sub>CO<sub>3</sub> (23 mg; 0.17 mmol) in MeCN (5 mL) was stirred at 85°C for 18 h. The reaction was cooled to RT and volatiles were removed in vacuo and partitioned between EtOAc and saturated aqueous NH<sub>4</sub>Cl. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc over 50 min) to give crude Part F compound.

An alternative procedure for the synthesis of Part F compound is as follows:

To a RT solution of Part E compound (700 mg; 2.0 mmol) and 5-phenyl-2-methyl-oxazole-4-ethanol (500 mg, 2.46 mmol) in toluene (15 mL) was added cyanomethylenetriethylphosphine (500  $\mu$ L; 2.0 mmol) dropwise. The mixture was heated at 88°C in an oil bath for 2 h, cooled to RT and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc over 50 min) to give Part F compound (800 mg; 75%). [M + H]<sup>+</sup> = 536.6

G.



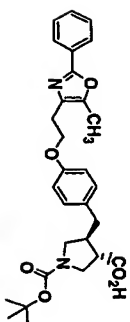
5 A solution of crude Part F compound and LiOH·H<sub>2</sub>O (25 mg; 0.61 mmol) in THF (2 mL), MeOH (1 mL) and H<sub>2</sub>O (0.3 mL) was stirred at 0°C for 2 h, then was quenched with saturated aqueous NH<sub>4</sub>Cl and concentrated in vacuo. The residue was partitioned between saturated aqueous NH<sub>4</sub>Cl and EtOAc.

10 The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 1) and lyophilized to give the title compound (5.0 mg; 7%) as a solid.

[M + H]<sup>+</sup> = 507.4

15 <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.85 (m, 2 H), 7.37 (m, 3 H), 6.99 (d, 2 H; J = 8.4 Hz), 6.77 (m, 2 H), 4.13 (m, 2 H), 3.51 (m, 1 H), 3.35 (m, 1 H), 3.15 (m, 2 H), 3.00 (m, 1 H), 2.87 (t, 2 H; J = 8.4 Hz), 2.70 (m, 1 H), 2.55 (m, 1 H), 2.32 (m, 1 H), 2.27 (s, 2 H), 1.35 (2S, 9 H).

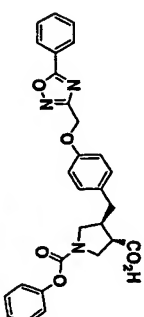
20 In addition, a second, later eluting fraction from the preparative HPLC of the above crude product was identified as the epimerized trans-isomer Example 24 compound (5.0 mg; 7%):



[M + H]<sup>+</sup> = 507.4

<sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.94 (m, 2 H), 7.4 (m, 3 H), 7.09 (d, 2 H; J = 6.4 Hz), 6.84 (d, J = 8.0 Hz, 2 H), 4.22 (m, 2 H), 3.60 (m, 1 H), 3.45 (m, 1 H), 3.35 (m, 1 H), 3.05 (m, 1 H), 2.95 (t, 2 H; J = 6.4 Hz), 1.80 (m, 2 H), 2.60 (m, 2 H), 2.37 (s, 3 H), 1.4 (s, 9 H).

#### Example 25

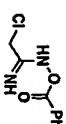


A.



15 To a vigorously stirred mixture of chloroacetonitrile (7.5 g; 0.10 mmol) and hydroxylamine hydrochloride (6.95 g; 0.10 mmol) in H<sub>2</sub>O (25 mL) was carefully added Na<sub>2</sub>CO<sub>3</sub> (5.3 g; 0.05 mmol) while maintaining the reaction temperature at ≤ 30°C. The mixture was then stirred at 30°C for 15 min, then was extracted with Et<sub>2</sub>O (2 x 80 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give Part A compound (6.9 g; 64%) as a white solid.

B.

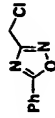


30 To a 0°C mixture of Part A compound (1.0 g; 9.0 mmol) and K<sub>2</sub>CO<sub>3</sub> (870 mg; 6.3 mmol) in acetone (45 mL) was added dropwise a solution of benzoyl chloride (1.0 mL;



9.0 mmol) in acetone (5 mL). The reaction was allowed to warm to RT and stirred at RT for 30 min. Volatiles were removed in vacuo and the residue was partitioned between H<sub>2</sub>O and EtOAc. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to give crude Part B compound (1.50 g; 76%) as a white solid.

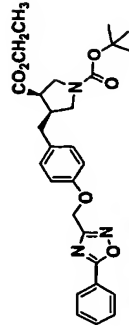
C.



10

A solution of crude Part B compound (1.50 g) in HOAc (25 mL) was heated to reflux for 1.5 h, after which volatiles were removed in vacuo. The residue was partitioned between H<sub>2</sub>O (40 mL) and EtOAc (50 mL); the organic phase was washed with H<sub>2</sub>O (2 x 40 mL), saturated aqueous NaHCO<sub>3</sub> (2 x 40 mL) and brine (40 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 4:1 to 7:3 hexane:EtOAc) to give Part C compound (840 mg; 61%) as a white solid.

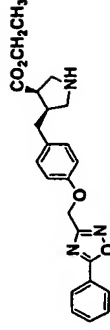
D.



25

A mixture of crude Part C compound (120 mg; 0.60 mmol), Example 23 Part E compound (100 mg; 0.30 mmol) and K<sub>2</sub>CO<sub>3</sub> (83 mg; 0.60 mmol) in MeCN (3 mL) was heated at 90°C for 8 h. After cooling to RT, the mixture was filtered. The filtrate was concentrated in vacuo and the residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 9:1 to 3:1 hex:EtOAc) to give Part D compound (140 mg; 96%) as a syrup. [M + H]<sup>+</sup> = 508.3; [M + Na]<sup>+</sup> = 530.3

E.

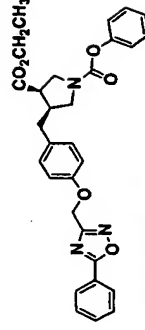


5

A solution of Part D compound (140 mg; 0.28 mmol) and HCl (700 µL of a 4 M solution in dioxane) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was stirred at RT for 2 h, then was concentrated in vacuo to give crude Part E compound (100 mg; 82%) as a white solid.

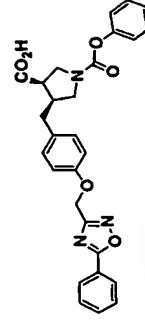
10

F.



A solution of crude Part E compound (25 mg; 0.056 mmol), phenyl chloroformate (9 µL; 0.067 mmol) and NaHCO<sub>3</sub> (24 mg; 0.28 mmol) in H<sub>2</sub>O and THF (2 mL each) was stirred at RT for 1 h, then was partitioned between H<sub>2</sub>O and EtOAc (3 mL each). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 9:1 to 3:1 hex:EtOAc) to give Part F compound (27 mg; 91%) as a white solid. [M + H]<sup>+</sup> = 528.2

G.



25

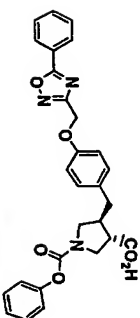
A solution of Part F compound (27 mg; 0.05 mmol) and LiOH.H<sub>2</sub>O (11 mg; 0.25 mmol) in THF and H<sub>2</sub>O (1 mL each) was stirred at RT overnight, then the pH was adjusted to ~3 with aqueous 1 N HCl. The mixture was partitioned between H<sub>2</sub>O and EtOAc. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 1:1 Solvent A:Solvent B to 100% B over 10 min was used, followed by 5 min hold at 100% B) to give two compounds. The compound with the shorter retention time was lyophilized from 1,4 dioxane to give the title compound (11 mg; 41%) as a white solid.

[M + H]<sup>+</sup> = 500.0

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.14 (m, 2 H), 7.65 (m, 1 H), 7.58 (m, 2 H), 7.35 (m, 2 H), 7.20 (m, 3 H), 7.08 (m, 2 H), 7.03 (m, 2 H), 5.24 (s, 2 H), 3.90 (m, 0.5 H), 3.75 (m, 1 H), 3.56 (m, 1 H), 3.29-3.50 (m, 2.5 H), 2.75-2.92 (m, 2H), 2.54 (m, 1 H)

The second compound (longer retention time) was determined to be the corresponding epimerized trans-isomer. This compound was lyophilized from dioxane to give Example 26 compound (6 mg; 23%) as a white solid.

#### Example 26

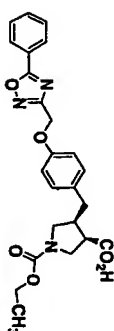


[M + H]<sup>+</sup> = 500.0

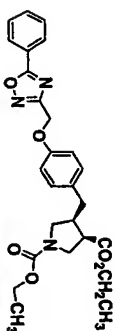
<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.14 (m, 2 H), 7.65 (m, 1 H), 7.58 (m, 2 H), 7.35 (m, 2 H), 7.20 (m, 3 H), 7.08 (m, 2 H), 7.03 (m,

2 H), 5.24 (s, 2 H), 3.90 (m, 0.5 H), 3.75 (m, 1 H), 3.65 (m, 1 H), 3.50 (m, 0.5 H), 3.32 (m, 0.5 H), 3.22 (m, 0.5 H) 2.85-2.97 (m, 2H), 2.78 (m, 1 H), 2.65 (m, 1 H).

#### Example 27

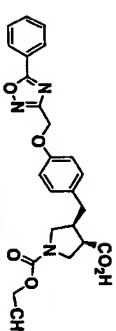


A.



Example 25 Part E compound (25 mg; 0.056 mmol) and ethyl chloroformate (7 μL; 0.067 mmol) were reacted (using the same experimental procedure as for the preparation of Example 25 Part F compound) to give Part A compound (20 mg; 74%) as a white solid. [M + H]<sup>+</sup> = 480.21

B.



A solution of Part A compound (20 mg; 0.042 mmol) and LiOH.H<sub>2</sub>O (9 mg; 0.21 mmol) in THF and H<sub>2</sub>O (1 mL each) was stirred at RT overnight, after which the pH was adjusted to ~3 with aqueous 1 N HCl. The mixture was partitioned between H<sub>2</sub>O and EtOAc. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 25) to give two compounds. The compound with the shorter

retention time was lyophilized from 1,4 dioxane to give the title compound (9.3 mg; 49%) as a white solid.

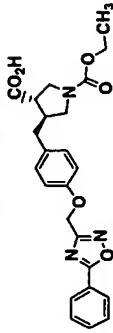
$[M + H]^+ = 452.1$

Analytical HPLC: retention time = 4.91 min (YMC S5 ODS 4.6 x 50 mm column; continuous gradient from 50:50 A:B to 100% B over 8 min; A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA; B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA; flow rate = 2.5 mL/min)

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.14 (m, 2 H), 7.65 (m, 1 H), 7.60 (m, 2 H), 7.14 (m, 2 H), 7.01 (m, 2 H), 5.24 (s, 2 H), 4.10 (m, 2 H), 3.68 (m, 1 H), 3.50 (m, 1 H), 3.20-3.33 (m, 2 H), 3.15 (m, 1 H), 2.85 (m, 1 H), 2.70 (m, 1 H), 2.45 (m, 1 H), 1.22 (m, 3 H)

The second compound (longer retention time) was determined to be the corresponding epimerized trans-isomer. This compound was lyophilized from dioxane to give Example 28 compound (3.2 mg; 17%) as a white solid.

#### Example 28



20

$[M + H]^+ = 452.0$

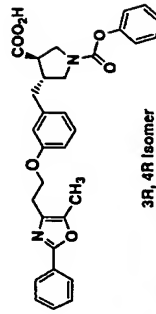
retention time = 5.14 min (YMC S5 ODS 4.6 x 50 mm column; continuous gradient from 50:50 A:B to 100% B over 8 min; A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA; B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA; flow rate = 2.5 mL/min)

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 8.14 (m, 2 H), 7.67 (m, 1 H), 7.59 (m, 2 H), 7.16 (m, 2 H), 7.01 (m, 2 H), 5.24 (s, 2 H), 4.08 (m, 2 H), 3.67 (m, 1 H), 3.55 (m, 1 H), 3.42 (m, 1 H), 3.10 (m, 1 H), 2.90 (m, 1 H), 2.82 (m, 1 H), 2.68 (m, 1 H), 2.60 (m, 1 H), 1.22 (m, 3 H)

35

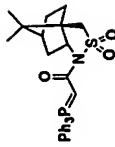
#### Example 29

- 156 -



3R, 4R isomer

A.

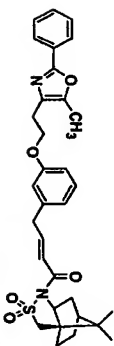


5

To a RT solution of L-(1R)-(+)-2,10-camphorsultam (1.0 g; 4.64 mmol) in anhydrous toluene (5 mL) under an atmosphere of N<sub>2</sub> was added Me<sub>3</sub>Al (3.0 mL of a 2.0 M solution in toluene; 6.0 mmol). The solution was stirred at RT for 2 h, after which Ph<sub>3</sub>P=CHCO<sub>2</sub>CH<sub>3</sub> (1.70 g; 5.0 mmol) was added. The reaction was stirred at 150°C in a sealed tube for 2 h, cooled to RT, and partitioned between H<sub>2</sub>O and EtOAc (50 mL each). The organic phase was washed with H<sub>2</sub>O (2 x 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; hexane:EtOAc 3:1) to give Part A compound (1.0 g; 39%) as an oil.

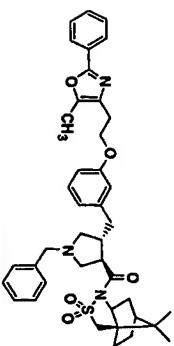
- 157 -

B.



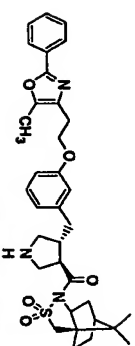
A solution of Part A compound (200 mg; 0.39 mmol) and the aldehyde (Example 1 Part E compound; 110 mg; 0.35 mmol) in toluene (20 mL) was heated at reflux for 2 h, then was concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; hex:EtOAc 3:1) to give Part B compound (51 mg; 23%) as an oil.

C.



To a solution of Part B compound (51 mg; 0.090 mmol) in toluene (2 mL) were successively added Example 1 Part B compound (36 mg; 0.15 mmol) and a catalytic amount of TFA (1  $\mu$ L). The reaction was stirred at RT for 3 h, then was partitioned between EtOAc (10 mL) and saturated aqueous NaHCO<sub>3</sub> (20 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; hex:EtOAc 3:1) to provide Part C compound (35 mg; 56%) as an oil.

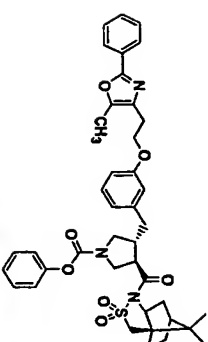
D.



25

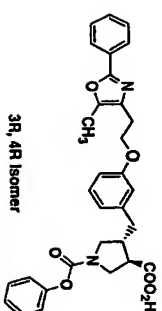
A mixture of Part C compound (35 mg; 0.058 mmol) and 10% Pd/C (5 mg) in MeOH (5 mL) and HOAc (200  $\mu$ L) was stirred under an atmosphere of H<sub>2</sub> (balloon) for 5 h. Solids were removed by filtration through Celite<sup>®</sup> and the filtrate was concentrated in vacuo to give Part D compound (25 mg; 71%) as an oil.

E.



A mixture of Part D compound (25 mg; 0.033 mmol), DMAP (13 mg; 0.1 mmol) and phenyl chloroformate (78 mg; 0.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was stirred at RT for 30 min, then was partitioned between EtOAc and H<sub>2</sub>O (20 mL each). The organic phase was washed with H<sub>2</sub>O and aqueous 1 M HCl (10 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hexane to 30:70 hexane:EtOAc over 25 min) to give Part E compound (17 mg; 57%) as an oil.

F.



3R, 4R isomer

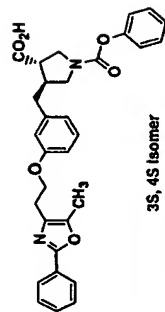
A solution of Part A compound (17 mg; 0.024 mmol) in aqueous 1 N LiOH (0.5 mL; 0.50 mmol) and THF (1.5 mL) was stirred at RT for 6 h, then was partitioned between

25

aqueous 1 N HCl (1 mL) and EtOAc (2 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 25) to give the title compound (6 mg; 47%) as a white solid.

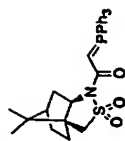
[M + H]<sup>+</sup> = 527.0

### Example 30



3S, 4S isomer

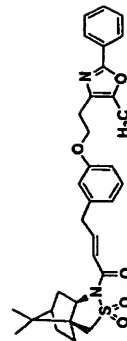
A.



15

D-(1S)-(-)-2,10-camphorsultam (1.0 g; 4.64 mmol) was reacted with Ph<sub>3</sub>P=CHCO<sub>2</sub>CH<sub>3</sub> (1.70 g; 5.0 mmol) and Me<sub>3</sub>Al (3 mL of a 2 M solution in toluene) in exactly the same way as Example 29 Part A to give Part A compound (1.0 g; 39%) as an oil.

B.

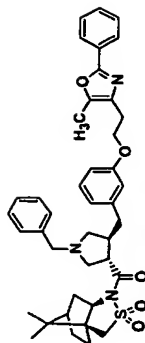


25

Part A compound (200 mg; 0.39 mmol) was reacted with the aldehyde Example 1 Part E compound (110 mg; 0.35

mmol) in the same way as Example 29 Part B to give Part B compound (45 mg; 20%) as an oil.

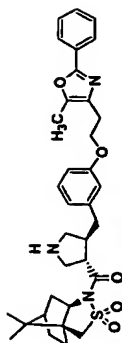
C.



5

Part B compound (45 mg; 0.08 mmol) was reacted with Example 1 Part B compound (36 mg; 0.15 mmol) in the same way as Example 29 Part C to give Part C compound (28 mg; 51%) as an oil.

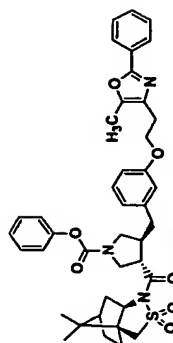
D.



15

Part C compound (28 mg; 0.046 mmol) was used (the same procedure as described in Example 29 Part D) to prepare Part D compound (20 mg; 72%) as an oil.

E.

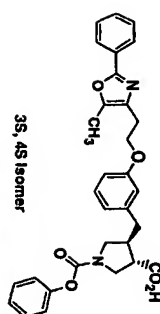


20

Part D compound (20 mg; 0.033 mmol) was reacted with phenyl chloroformate (78 mg; 0.50 mmol) in the same manner as Example 29 Part E to provide Part E compound (18 mg; 75%) as an oil.

25

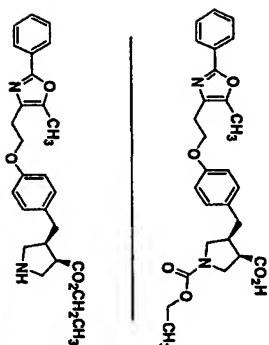
F.



Part E compound (18 mg; 0.025 mmol) was treated with aqueous LiOH (0.5 mL of a 1 M solution) in the same manner as Example 29 Part F to provide the title compound (7 mg; 53%) as a solid.  
 $[M + H]^+ = 527.0$

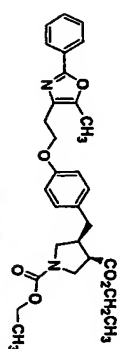
Example 31

A.



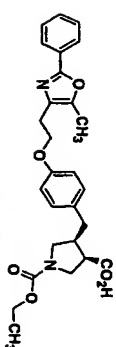
To a RT solution of Example 23 Part F compound (30 mg; 0.056 mmol) in  $CH_2Cl_2$  (1 mL) was added HCl (250  $\mu$ L of a 4 M solution in dioxane). The reaction was stirred at RT for 30 min, then was concentrated in vacuo to give crude Part A compound.

B.



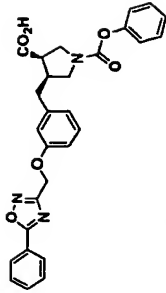
A mixture of crude Part A compound, ethyl chloroformate (50  $\mu$ L; 0.52 mmol), THF (5 mL) and saturated aqueous  $NaHCO_3$  (sufficient to adjust the pH to -9) was stirred at RT for 30 min, then was concentrated in vacuo. The residue was partitioned between  $H_2O$  and  $Et_2O$ . The aqueous phase was extracted with  $Et_2O$ ; the combined organic extracts were dried ( $MgSO_4$ ) and concentrated in vacuo to give crude Part B compound (25 mg; 76%) as an oil.

C.

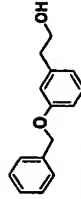


A mixture of Part B compound (5 mg; 0.01 mmol) in HOAc (500  $\mu$ L) and aqueous HCl (150  $\mu$ L of a 20% solution) was stirred at 80°C for 18 h, then was cooled to RT and concentrated in vacuo. The residue was partitioned between  $EtOAc$  and saturated aqueous  $NH_4Cl$ . The organic phase was dried ( $Na_2SO_4$ ) and concentrated in vacuo. The residue was lyophilized from dioxane to give the title compound (5 mg; 100%) as an oil.  
 $[M + H]^+ = 478.2$

30

Example 32

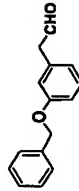
5 A.



A mixture of 3-hydroxyphenyl ethanol (30.0 g; 0.217 mol), benzyl bromide (28.4 mL; 0.239 mol) and  $K_2CO_3$  (45 g; 0.326 mol) in MeCN (500 mL) was stirred at RT for 48 h, then was filtered. The filtrate was concentrated in vacuo; the residue was recrystallized from hexane to give Part A compound (49 g; 99%) as a white solid.

15

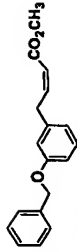
B.



To a mixture of Part A compound (40 g; 175 mmol) and Florisil (180 g) in  $CH_2Cl_2$  (1 L) was added pyridinium chlorochromate (40 g; 186 mmol) in portions. The reaction was stirred at RT for 3.5 h, then was filtered through Florisil. To the filtrate was added more pyridinium chlorochromate (20 g; 93 mmol) and Florisil (70 g). The reaction was stirred at RT for another 2 h, then was filtered through Florisil. The filtrate was concentrated in vacuo to give crude Part B compound (34 g; 86%) as an oil.

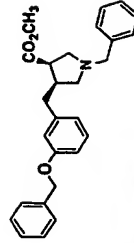
- 164 -

C.



To a  $-78^\circ C$  solution of  $(CF_3CH_2O)_2POCH_2CO_2CH_3$  (29.1 g; 91.5 mmol) and 18-crown-6 (25 g; 95.4 mmol) in anhydrous THF (600 mL) under Ar was added dropwise  $KN(TMS)$  (186 mL of a 1 M solution in toluene). The reaction was stirred at  $-78^\circ C$  for 10 min, after which a solution of Part B compound (17.3 g; 76.5 mmol) in THF (100 mL) was added dropwise by cannula over 15 min. The reaction was stirred at  $-78^\circ C$  for 2 h, then was quenched by cautious slow addition of saturated aqueous  $NH_4Cl$  (150 mL). The mixture was allowed to warm to RT, then extracted with EtOAc. The organic phase was washed with  $H_2O$  (150 mL), dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; stepwise gradient from 10:1 to 4:1 hex:EtOAc) to remove the crown ether. The crude product was chromatographed ( $SiO_2$ ; continuous gradient from 10:1 to 5:1 hex:EtOAc) to give Part C compound (6.5 g; 30%) as a pale yellow oil.

D.

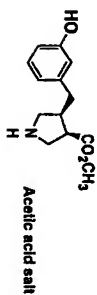


To a  $0^\circ C$  solution of Part C compound (3.90 g; 13.8 mmol) and Example 1 Part B compound (5.0 g; 20.7 mmol) in toluene (40 mL) was added TFA (200  $\mu L$ ) dropwise. The reaction was stirred at  $0^\circ C$  for 30 min, then was partitioned between EtOAc (150 mL) and saturated aqueous  $NaHCO_3$  (100 mL). The organic phase was washed with brine (100 mL), dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; continuous

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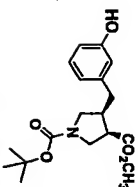
gradient from 4:1 to 1:1 hex:EtOAc) to give Part D compound (5.50 g; 96%) as an oil.

E.



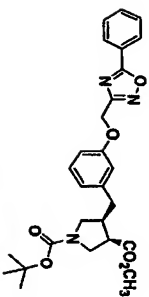
A mixture of Part D compound (5.50 g; 13.3 mmol), 10% Pd/C (300 mg) and HOAc (1.13 mL; 20 mmol) in EtOH (100 mL) was stirred an atmosphere of H<sub>2</sub> (balloon) for 26 h. The catalyst was filtered off (celite®) and the filtrate was concentrated in vacuo to give Part E compound (3.60 g; 92%) as an oil.

F.



A mixture of Part E compound (3.60 g; 12.2 mmol), di-tert butyl dicarbonate (2.66 g; 24.4 mmol) and NaHCO<sub>3</sub> (2.05 g; 24.4 mmol) in THF and H<sub>2</sub>O (100 mL each) was stirred at RT for 1 h, then was partitioned between EtOAc (150 mL) and H<sub>2</sub>O (100 mL). The organic phase was washed with brine (100 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 4:1 to 3:2 hex:EtOAc) to give Part F compound (3.70 g; 91%) as a syrup.

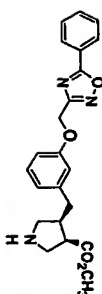
G.



- 166 -

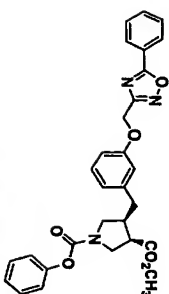
A mixture of Part F compound (150 mg; 0.43 mmol), Example 25 Part C compound (120 mg; 0.62 mmol), and K<sub>2</sub>CO<sub>3</sub> (118 mg; 0.86 mmol) in MeCN (6 mL) was heated at 80°C for 16 h, then was cooled to RT and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 9:1 to 7:3 hex:EtOAc) to give Part G compound (200 mg; 94%) as a syrup.

H.



A mixture of Part G compound (200 mg; 0.41 mmol) in HCl/dioxane (1.0 mL of a 4 M solution) and CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was stirred at RT for 1 h, then was concentrated in vacuo to give Part H compound (165 mg; 92%) as a white solid which was used in the next step without further purification.

I.

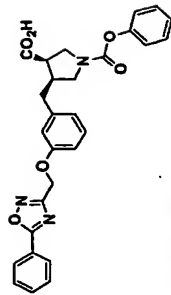


A mixture of Part H compound (23 mg; 0.052 mmol), phenyl chloroformate (8 µL; 0.062 mmol) and NaHCO<sub>3</sub> (22 mg; 0.26 mmol) in THF and H<sub>2</sub>O (1 mL each) was stirred at RT for 1 h, then was partitioned between H<sub>2</sub>O (5 mL) and EtOAc (10 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 25) to give Part I compound (20 mg; 75%) as a colorless syrup.

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J.

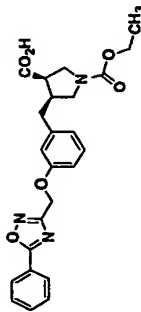


5

A mixture of Part I compound (20 mg; 0.039 mmol) in conc. HCl (0.2 mL) and HOAc (1 mL) was heated at 70°C for 18 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 25) and lyophilized from dioxane to give the title compound (10 mg; 51%) as a white solid.  $[M + H]^+ = 500.0$

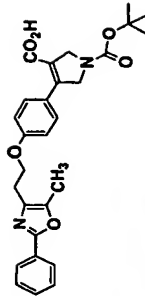
Example 33

15



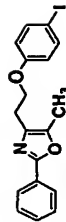
Example 32 Part H compound (23 mg; 0.052 mmol) and ethyl chloroformate (6  $\mu$ L; 0.062 mmol) were reacted (using the same 2-step sequence as described for the synthesis of Example 32) to give the title compound (7.7 mg; 33% for 2 steps) as a white solid.  $[M + H]^+ = 452.0$

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Example 34

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A.

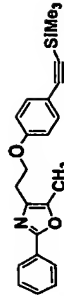


A mixture of 4-iodophenol (3.27 g; 14.9 mmol),  $K_2CO_3$  (3 g; 21.7 mmol) and the mesylate Example 47 Part A compound (3.0 g; 10.7 mmol) in MeCN (50 mL) was heated at reflux overnight under  $N_2$ . The reaction was cooled to RT and partitioned between EtOAc and  $H_2O$  (200 mL each). The organic phase was washed with aqueous NaOH (2 x 20 mL of a 1 M solution) and  $H_2O$ , dried ( $Na_2SO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; continuous gradient from 100% hex to 7:3 hex:EtOAc over 20 min, then at 7:3 hex:EtOAc for 15 min) to give Part A compound (2.50 g; 57%) as a white solid.

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B.

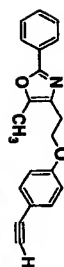


A mixture of Part A compound (2.24 g; 5.53 mmol),  $Cu(I)I$  (42 mg; 0.221 mmol),  $(Ph_3P)_2PdCl_2$  (78 mg; 0.11 mmol),  $K_2CO_3$  (3.05 g; 22.1 mmol) and trimethylsilylacetylene (3.9 mL; 27.7 mmol) in THF (20 mL) was stirred at RT in a sealed tube for 60 h. The dark mixture was filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed

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(SiO<sub>2</sub>; continuous gradient from 100% hex to 4:1 hex:EtOAc over 25 min, then at 4:1 hex:EtOAc for 10 min) to give Part B compound (2.04 g; 98%) as a brown solid.

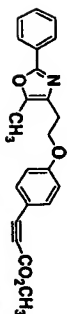
5 C.



10 A solution of Part B compound (2.04 g; 5.44 mmol) and tetrabutylammonium fluoride (5.44 mL of a 1 M solution in THF) in THF (60 mL) was stirred at RT for 30 min, then was concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 100% hex to 3:1 hex:EtOAc) to give Part C compound (1.50 g; 91%) as a slightly yellow solid.

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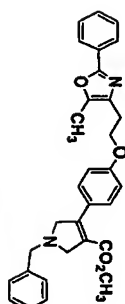
D.



To a -78°C solution of Part C compound (875 mg; 2.89 mmol) in THF (10 mL) was added dropwise methylolithium (3.0 mL of a 1.4 M solution in Et<sub>2</sub>O; 4.20 mmol). The reaction was stirred at -78°C for 30 min, after which dimethyl carbonate (900  $\mu$ L; 10.6 mmol) was added dropwise. Stirring was continued at -78°C for 30 min, after which the reaction was allowed to warm to RT (30 min) and stirred at RT for 30 min. Excess saturated aqueous NH<sub>4</sub>Cl was added to quench the reaction and the mixture was partitioned with EtOAc (150 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; gradient from 100% hex to 3:1 hex:EtOAc over 10 min; 3:1 hex:EtOAc for 5 min, gradient from 3:1 to 2:1 hex:EtOAc over 5 min, then at

2:1 hex:EtOAc for 10 min) to give Part D compound (800 mg; 77% as a white solid).

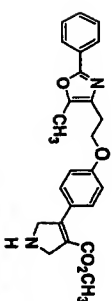
E.



To a RT solution of Part D compound (700 mg; 2.2 mmol) in toluene (5 mL) were successively added TFA (100  $\mu$ L) and Example 1 Part B compound (678 mg; 2.86 mmol) over 2 min. The reaction was stirred at RT for 10 min, after which additional Example 1 Part B compound (290 mg; 1.23 mmol) was added over 15 min. A final aliquot of Example 1 Part B compound (290 mg; 1.23 mmol) was added over 30 min. At this point (by analytical HPLC) there was 53% desired product, 15% of the bis-addition adduct and 12% unreacted starting material. The mixture was partitioned between EtOAc and saturated NaHCO<sub>3</sub> (20 mL each). The organic phase was concentrated in vacuo and chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 85:15 hex:EtOAc over 15 min, 85:15 hex:EtOAc for 3 min, then continuous gradient from 85:15 to 3:2 hex:EtOAc over 5 min, then at 3:2 hex:EtOAc for 5 min) to give Part E compound (596 mg; 62%) as an viscous oil.

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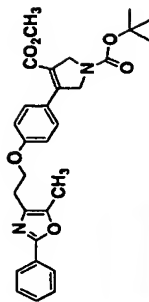
F.



To a -78°C solution of Part E compound (122 mg; 0.247 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added CH<sub>3</sub>CHClCOCl (53

μL; 0.49 mmol) dropwise. The mixture was stirred at -78°C for 30 min, then was warmed to RT and stirred at RT for 3 h, then concentrated in vacuo. The residue was dissolved in MeOH (3 mL) and the mixture was stirred at RT for 72 h, then concentrated in vacuo to give crude Part F compound as a foam which was used in the next step without further purification.

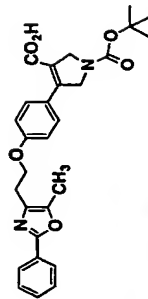
G.



10

A mixture of crude Part F compound, NaHCO<sub>3</sub> (84 mg; 1.0 mmol) and di-tert butyl dicarbonate (84 mg; 0.38 mmol) in THF/H<sub>2</sub>O (3 mL of a 1:1 solution) was stirred at RT for 2 h, then was partitioned between EtOAc and H<sub>2</sub>O (20 mL). The organic phase was concentrated in vacuo and the residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 85:15 hex:EtOAc over 10 min, 85:15 hex:EtOAc for 3 min, 85:15 to 3:2 hex:EtOAc over 10 min and 3:2 hex:EtOAc for 5 min) to give Part G compound (55 mg; 44% for 2 steps) as an oil. In addition Part E compound (30 mg; 25%) was also recovered.

H.



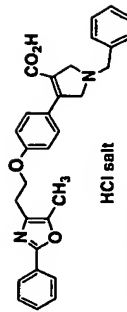
25

A mixture of Part G compound (55 mg; 0.11 mmol) and LiOH.H<sub>2</sub>O (10 mg; 0.23 mmol) in THF/H<sub>2</sub>O (1.6 mL of a

- 172 -

1:1 solution) was stirred at RT for 16 h, after which the pH was adjusted to ~5 by addition of aqueous 1 M HCl. The mixture was extracted with EtOAc (10 mL). The organic phase was concentrated in vacuo, and the residue was chromatographed (SiO<sub>2</sub>; 3:1 hex:EtOAc, then 100% EtOAc, then 10:1 EtOAc:MeOH) to give the title compound (45 mg; 80%) as a foam.  
[M + H]<sup>+</sup> = 491

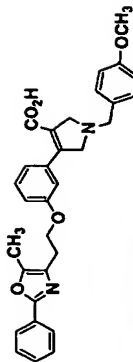
10

Example 35

HCl salt

A mixture of Example 34 Part E compound (20 mg; 0.040 mmol) and LiOH.H<sub>2</sub>O (8 mg; 0.19 mmol) in THF/H<sub>2</sub>O (1.6 mL of a 1:1 solution) was stirred at RT for 20 h, after which the pH was adjusted to ~5 with aqueous 1 M HCl. The THF was removed in vacuo and the mixture was extracted with EtOAc (10 mL). The organic phase was concentrated in vacuo to give a white solid, which was further purified by crystallization from MeOH. This material was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and HCl in dioxane (4 drops of a 4 N solution) was added. Volatiles were removed in vacuo to give the title compound (10 mg; 48%) as a white solid. [M + H]<sup>+</sup> = 481

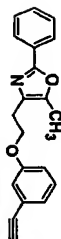
25

Example 36

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- 173 -

A.



5 A mixture of 3-hydroxyphenylacetylene (1.0 g; 8.46 mmol),  $K_2CO_3$  (4.0 g; 30 mmol) and the mesylate Example 47 Part A compound (3.0 g; 10.7 mmol) in MeCN (10 mL) was heated at 90°C for 5 h under  $N_2$ . The reaction was cooled to RT and the solids were filtered off; the filtrate was 10 partitioned between EtOAc and  $H_2O$  (100 mL each). The organic phase was washed with aqueous HCl and NaOH (10 mL each of a 1 M solution), dried ( $Na_2SO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; 3:1 hex:EtOAc) to give Part A compound (1.25 g; 49%) as white 15 crystals.

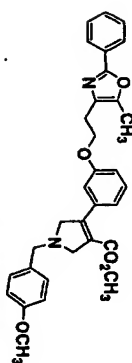
B.



20 To a -78°C solution of Part A compound (1.09 g; 3.59 mmol) in anhydrous THF (10 mL) was added methylolithium (3.2 mL of a 1.4 M solution in Et<sub>2</sub>O) dropwise. The reaction was stirred at -78°C for 2 h, 25 after which anhydrous dimethyl carbonate (1 mL; 12 mmol) was added in one portion. The reaction was allowed to warm to RT and stirred at RT for 30 min, after which saturated aqueous  $NH_4Cl$  (5 mL) was added. The mixture was partitioned between EtOAc and  $H_2O$  (50 mL each). The 30 organic phase was washed with  $H_2O$  (2 x 50 mL), dried ( $Na_2SO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; 3:1 hexane:EtOAc) to give Part B compound (1.07 g; 83%) as an oil.

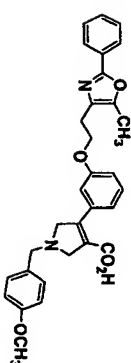
- 174 -

C.



5 A mixture of Part B compound (1.07 g; 3.0 mmol), Example 17 Part D compound (0.79 g; 3.0 mmol) and TPA (1 drop) in toluene (10 mL) was stirred at RT for 3 h, then was concentrated in vacuo. The residue was 10 chromatographed ( $SiO_2$ ; hex:EtOAc 1:1) to give Part C compound (1.01 g; 64%) as white crystals.

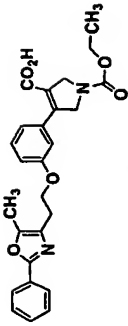
D.



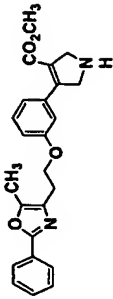
15 A solution of Part C compound (500 mg; 0.953 mmol) in HOAc/concentrated HCl (5 mL of a 4:1 solution) was stirred at 66°C for 30 h. The reaction was cooled to RT and partitioned between ice water (100 mL) and EtOAc (20 20 mL). The aqueous phase was extracted with EtOAc (2 x 20 mL); the combined organic extracts were washed with  $H_2O$  (2 x 50 mL), pH4 aqueous buffer (50 mL), dried ( $Na_2SO_4$ ), and concentrated in vacuo to a volume of ~ 5 mL. The precipitate was filtered off and dried in vacuo to give 25 the title compound (310 mg; 63%) as a white solid.  $[M + H]^+ = 511.2$

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Example 37

A.

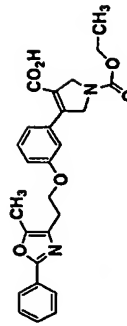


5

To a -78°C solution of Example 36 Part C compound (474 mg; 0.90 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (0.5 mL) was added  $\text{CH}_3\text{CHClOCCl}$  (140  $\mu\text{L}$ ; 1.8 mmol). The reaction mixture was stirred at -78°C for 30 min, then was warmed to -20°C and stirred at -20°C for 1 h. Volatiles were removed in vacuo and MeOH (10 mL) was added; the solution was then stirred at RT for 8 h. Volatiles were removed in vacuo to give crude Part A compound (450 mg; 99%) as an oil which was used in the next step without further purification.

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B.



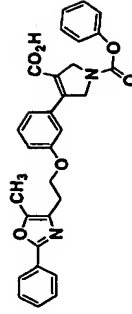
20

To a 0°C solution of Part A compound (50 mg; 0.123 mmol) in THF (1 mL) was added saturated aqueous  $\text{NaHCO}_3$  (1 mL), followed by ethyl chloroformate (22 mg; 0.20 mmol). The reaction was stirred at 0°C for 15 min, then was partitioned between EtOAc and  $\text{H}_2\text{O}$  (5 mL each). The organic phase was washed with  $\text{H}_2\text{O}$  (5 mL), dried ( $\text{MgSO}_4$ )

25

and concentrated in vacuo. A mixture of this crude carbamate-ester and acetic acid/concentrated HCl (4:1) was heated at 80°C for 18 h; the reaction was cooled to RT and concentrated in vacuo. The mixture was extracted with EtOAc (10 mL). The organic phase was concentrated in vacuo, and the residue was purified by preparative HPLC (as described for Example 1) to give the title compound (10 mg; 17%) as a white solid.

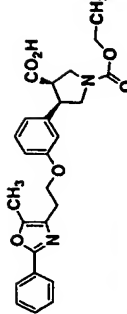
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Example 38

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The title compound (16 mg; 26%) was prepared from Example 37 Part A compound (50 mg; 0.123 mmol) using the same sequence as for Example 37 except that phenyl chloroformate (31 mg; 0.20 mmol) was used instead of ethyl chloroformate.

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Example 39

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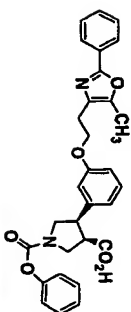
A suspension of Example 37 compound (5 mg; 0.011 mmol) and 10% Pd/C (5 mg) in MeOH (2 mL) was stirred at RT under an atmosphere of  $\text{H}_2$  (balloon) for 2 h. The catalyst was filtered off using Celite® and the filtrate was concentrated in vacuo. The residue was purified by

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preparative HPLC (as described for the purification of Example 1) to give the title compound (1.0 mg; 20%) as a white solid.

$$[\text{M} + \text{H}]^+ = 465.2$$

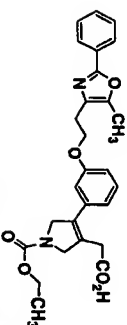
### Example 40



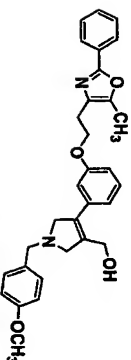
The title compound (3.0 mg; 60%) was prepared from Example 38 compound (5 mg; 0.0098 mmol) according to the procedure described for the synthesis of Example 39.

$[M + H]^+ = 513.2$

### Example 41



A.

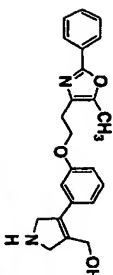


To a  $-70^{\circ}\text{C}$  solution of Example 36 compound (500 mg, 0.952 mmol) in anhydrous THF (10 mL) was added dropwise DIBALH (2.4 mL of a 1 M solution in hexane; 2.4 mmol).

25 The reaction was stirred at  $-70^{\circ}\text{C}$  for 20 min, then was warmed to RT and stirred at RT for 2 h, then cooled to  $-70^{\circ}\text{C}$  and finally quenched by dropwise addition of MeOH (1

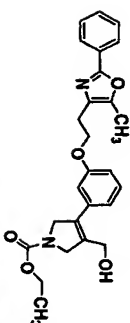
5. The mixture was allowed to warm to RT, then aqueous Rochelle salt (10 mL of a 1 M solution) was added and stirring was continued for 1 h. The mixture was partitioned between H<sub>2</sub>O and Et<sub>2</sub>O (20 mL each). The aqueous phase was extracted with additional Et<sub>2</sub>O (20 mL); the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; EtOAc:hex:Et<sub>3</sub>N 3:1:0.08) to give Part A compound (374 mg; 79%) as an oil.

B.



To a -78°C solution of Part A compound (261 mg; 15 0.53 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added CH<sub>3</sub>CHClOCCl (143 mg; 1.0 mmol). The reaction mixture was stirred at -78°C for 30 min, then was allowed to warm to RT and stirred at RT for 1 h. At this point, HPLC indicated that all starting material had been consumed. Volatiles were removed in vacuo and MeOH (10 mL) was added; the solution was then stirred at RT for 8 h. Volatiles were removed in vacuo to give crude Part B compound (100 mg; 51%) as an oil which was used in the next step without further purification.

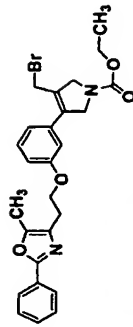
9.



A solution of crude Part B compound (100 mg; 0.27 mmol) and ethyl chloroformate (47  $\mu$ L; 0.50 mmol) in saturated aqueous  $\text{NaHCO}_3$  (2 mL) and THF (1 mL) was stirred at 0°C for 15 min, then was partitioned between  $\text{H}_2\text{O}$  and EtOAc (5 mL each). The organic phase was washed with  $\text{H}_2\text{O}$  (5 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for the purification of Example 1) to give Part C compound (30 mg; 25%) as an oil.

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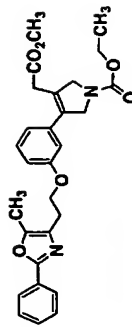
D.



To a 0°C mixture of Part C compound (30 mg; 0.067 mmol) and polyvinylpyrrolidone (300 mg) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was added phosphorus tribromide (134  $\mu$ L of a 1 M solution in  $\text{CH}_2\text{Cl}_2$ ; 0.134 mmol) dropwise over 5 min. The reaction was allowed to warm to RT and stirred at RT for 30 min, then was filtered. The filtrate was partitioned between  $\text{CH}_2\text{Cl}_2$  (20 mL) and  $\text{H}_2\text{O}$  (50 mL). The organic phase was washed with saturated aqueous  $\text{NaHCO}_3$  (2 x 20 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; hex:EtOAc 3:1) to give Part D compound (13 mg; 38%) as an oil.

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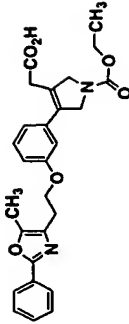
E.



A mixture of Part D compound (13 mg; 0.025 mmol),  $(\text{Ph}_3\text{P})_4\text{Pd}^0$  (5 mg;  $4.3 \times 10^{-3}$  mmol) and  $\text{K}_2\text{CO}_3$  (100 mg; 1.0 mmol) in anhydrous MeOH (5 mL) in an autoclave was pressurized to 100 psi with carbon monoxide (flushed 3X with CO). The reaction mixture was stirred at RT for 3 days, after which the CO gas was released and the mixture was filtered. The filtrate was concentrated in vacuo and the residue was chromatographed ( $\text{SiO}_2$ ; 3:1 hex:EtOAc) to give Part E compound (9.3 mg; 76%) as an oil.

10

F.



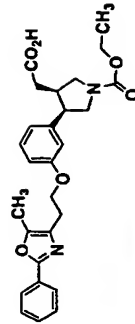
15

A mixture of Part E compound (9.3 mg; 0.019 mmol) and aqueous LiOH (0.5 mL of a 1 N solution) in THF (1 mL) was stirred at RT for 2 h, after which the reaction was partitioned between EtOAc (10 mL) and aqueous 1 M HCl (5 mL). The organic phase was washed with  $\text{H}_2\text{O}$  (3 x 10 mL) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1) to give the title compound (8.3 mg; 92%) as an oil.

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[M + H]<sup>+</sup> = 477.2

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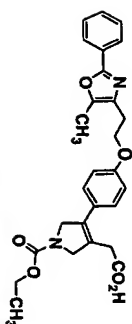
Example 42

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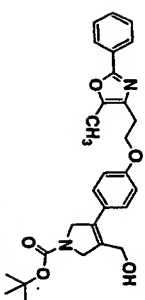
A suspension of Example 41 compound (4 mg; 0.01 mmol) and 10% Pd/C (2 mg) in MeOH (1 mL) was stirred at RT under an atmosphere of H<sub>2</sub> (balloon) for 2 h. The catalyst was filtered off on Celite® and the filtrate was concentrated in vacuo to give the title compound (3 mg; 60%) as a white solid.

[M + H]<sup>+</sup> = 479.2

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Example 43

A.



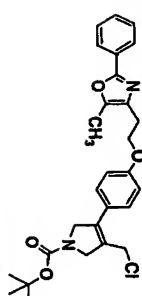
15

To a -78°C solution of Example 34 Part G compound (420 mg; 0.833 mmol) in anhydrous THF (8 mL) under argon was added dropwise DIBALH (1.8 mL of a 1 M solution in hexane; 1.8 mmol). The reaction was stirred at -78°C for 5 min, then was allowed to warm to RT and stirred at RT for 30 min. Since starting material still remained, the reaction was cooled to -78°C and more DIBALH (0.4 mL of a 1 M solution in hexane; 0.4 mmol) was added, after which the reaction was warmed to RT and stirred at RT for 1.5 h. The reaction was cooled to -78°C and MeOH (0.5 mL) was added dropwise, followed by Rochelle's salt (2.35 g in 10 mL H<sub>2</sub>O). The mixture was allowed to warm to RT and

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stirred at RT for 1.5 h, after which EtOAc (20 mL) was added and stirring was continued for 10 min. The organic phase was concentrated in vacuo and chromatographed (SiO<sub>2</sub>; 2:1 to 1:2 hex:EtOAc, then 100% EtOAc) to give Part A compound (352 mg; 88%) as a solid foam.

B.

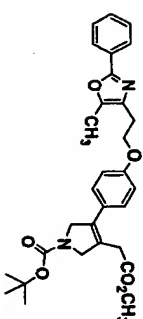


10

To a RT solution of Part A compound (25 mg; 0.053 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) was added CCl<sub>4</sub> (35 mg; 0.228 mmol) and Ph<sub>3</sub>P (24 mg; 0.092 mmol). The reaction was stirred at RT overnight and concentrated in vacuo; the residue was chromatographed (SiO<sub>2</sub>; hex to 2:1 hex:EtOAc) to give Part B compound (10 mg; 38%) as an oil.

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C.



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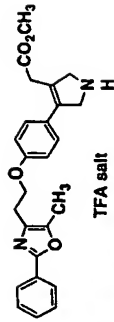
To a mixture of (Ph<sub>3</sub>P)<sub>4</sub>Pd<sup>+</sup> (9 mg; 0.0078 mmol) and KHCO<sub>3</sub> (50 mg; 0.50 mmol) in anhydrous MeOH (1 mL) was added a solution of Part C compound (10 mg; 0.020 mmol) in EtOAc (0.8 mL). The reaction mixture was placed in an autoclave and pressurized to 100 psi with carbon monoxide. The reaction mixture was stirred at RT for 2 h, after which the CO gas was released and the mixture was filtered. The filtrate was concentrated in vacuo and

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the residue was chromatographed (SiO<sub>2</sub>; 2:1 hex:EtOAc) to give Part C compound (8 mg; 76%) as an oil.

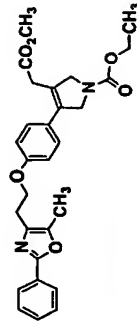
D.



5

A solution of Part C compound (12 mg; 0.023 mmol) in TFA (0.2 mL) and CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at RT for 2.5 h, then was concentrated in vacuo to give Part D compound as an oil, which was used in the next step without further purification.

E.

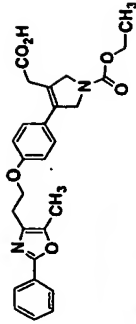


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To a solution of Part D compound in THF (0.7 mL) was added a solution of NaHCO<sub>3</sub> (8 mg; 0.095 mmol) in H<sub>2</sub>O (0.7 mL), followed by ethyl chloroformate (3 μL; 0.030 mmol). The reaction was stirred at RT for 2.5 h, then partitioned between EtOAc and H<sub>2</sub>O (10 mL each). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 2:1 hex:EtOAc) to give Part E compound (9.5 mg; 84% for 2 steps) as an oil.

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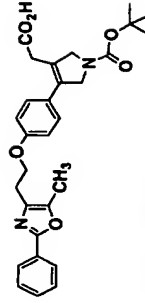
F.



A mixture of Part E compound (9.5 mg; 0.019 mmol) and LiOH·H<sub>2</sub>O (7 mg; 0.17 mmol) in THF/H<sub>2</sub>O (1.4 mL of a 1:1 solution) was stirred at RT for 2 h, after which the pH was adjusted to -5 with aqueous 1 M HCl. The mixture was extracted with EtOAc (10 mL). The organic phase was concentrated in vacuo, and the residue was chromatographed (SiO<sub>2</sub>; 1:1 hex:EtOAc, 100% EtOAc, then 10:1 EtOAc:MeOH), then further purified by preparative HPLC (conditions as described for Example 1 compound, except that a continuous gradient from 30:70 A:B to 100% B over 10 min was used) to give the title compound (4.2 mg; 46%) as a white foam.

$$[M + H]^+ = 477$$

#### Example 44



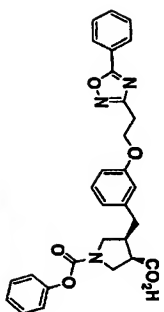
20

A mixture of Example 43 Part C compound (10 mg; 0.019 mmol) and LiOH·H<sub>2</sub>O (2 mg; 0.048 mmol) in THF/H<sub>2</sub>O (1.4 mL of a 1:1 solution) was stirred at RT for 16 h, after which the pH was adjusted to -5 with aqueous 1 M HCl. The mixture was extracted with EtOAc (10 mL). The organic phase was concentrated in vacuo, and the residue was chromatographed (SiO<sub>2</sub>; 3:1 hex:EtOAc, then 100%

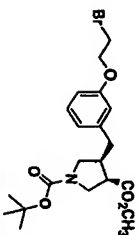
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EtOAc, then 10:1 EtOAc:MeOH) to give the title compound (6 mg; 62%) as a foam.  $[M + H]^+ = 504.2$

#### Example 45

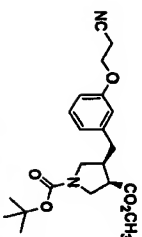


A.



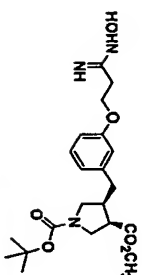
A mixture of Example 32 Part F compound (1.20 g; 3.6 mmol),  $K_2CO_3$  (1.0 g; 7.2 mmol) and 1,2-dibromoethane (3.1 mL; 36 mmol) in MeCN (50 mL) was heated at reflux for 46 h. Two additional portions of  $K_2CO_3$  (0.5 g at 12 & 36 h) were added during this time. The reaction was cooled to RT and filtered; the filtrate was concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; continuous gradient from 100% hex to 3:7 hex:EtOAc) to give Part A compound (1.10 g; 70%) as a syrup.

B.



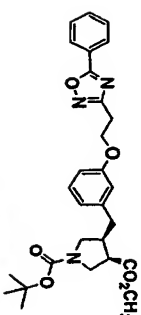
A mixture of Part A compound (1.05 g; 2.4 mmol) and tetrabutylammonium cyanide (1.27 g; 4.8 mmol) in  $CH_2Cl_2$  (25 mL) was stirred at RT for 18 h, then was concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; stepwise gradient from 4:1 to 3:2 hex:EtOAc) to give Part B compound (900 mg; 98%) as a syrup.  $[M + Na]^+ = 411.2$

C.



A mixture of Part B compound (200 mg; 0.52 mmol), aqueous  $NH_4OH$  (136 mg of a 50% solution) in MeOH (6 mL) and  $H_2O$  (3 mL) was stirred at 95°C for 3 h, then was cooled to RT and concentrated in vacuo. The residue was partitioned between  $H_2O$  and EtOAc; the organic phase was dried ( $MgSO_4$ ) and concentrated in vacuo to give crude Part C compound (200 mg; 92%) as a white solid, which was used in the next step without further purification.  $[M + H]^+ = 422.3$

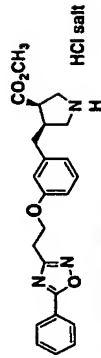
D.



A mixture of Part C compound (90 mg; 0.22 mmol) and benzoyl chloride (30  $\mu$ L; 0.26 mmol) in pyridine (5

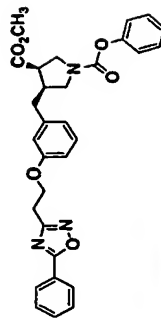
mL) was stirred at reflux for 4 h, then was cooled to RT and concentrated in vacuo. The residue was partitioned between EtOAc (10 mL) and H<sub>2</sub>O (5 mL); the organic phase was washed with brine (5 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 9:1 to 5:1 hex:EtOAc) to give Part D compound (70 mg; 65%) as a syrup.  
 [M + H]<sup>+</sup> = 508.3

10 E.



A mixture of Part D compound (70 mg; 0.14 mmol) in HCl/dioxane (1 mL of a 4 M solution; 4.0 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was stirred at RT for 2.5 h, then was concentrated in vacuo to give Part E compound (50 mg; 79%), which was used in the next step without further purification.

F.

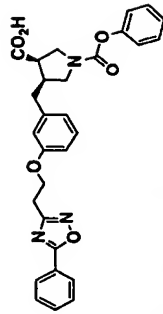


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A mixture of Part E compound (25 mg; 0.055 mmol), phenyl chloroformate (8  $\mu$ L; 0.11 mmol) and NaHCO<sub>3</sub> (23 mg; 0.28 mmol) in THF/H<sub>2</sub>O (2 mL of a 1:1 solution) was stirred at RT for 1 h, then was partitioned between EtOAc and H<sub>2</sub>O (5 mL each). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for the purification of

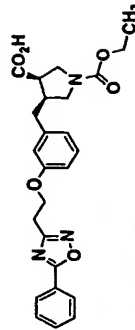
Example 26) to give Part F compound (19 mg; 66%) as a syrup. [M + H]<sup>+</sup> = 528.2

G.



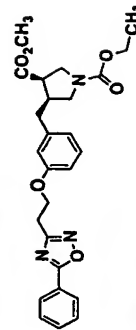
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A mixture of Part F compound (19 mg; 0.036 mmol) in concentrated HCl/glacial HOAc (2 mL of a 1:4 solution) was stirred at 70°C for 16 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for the purification of Part F compound) and lyophilized from dioxane to give the title compound (17 mg; 92%) as a white solid.

15 [M + H]<sup>+</sup> = 514.2Example 46

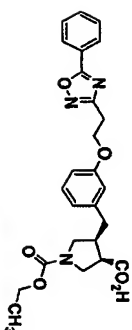
20

A.



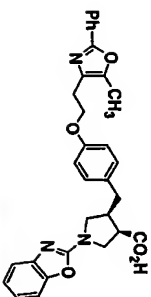
A mixture of Example 45 Part E compound (25 mg; 0.055 mmol), phenyl chloroformate (6  $\mu$ L; 0.11 mmol) and  $\text{NaHCO}_3$  (23 mg; 0.28 mmol) in THF/ $\text{H}_2\text{O}$  (2 mL of a 1:1 solution) was stirred at RT for 1 h, then was partitioned between EtOAc and  $\text{H}_2\text{O}$  (5 mL each). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for the purification of Example 26) to give Part A compound (18 mg; 69%) as a syrup.  $[M + H]^+ = 480.2$

B.

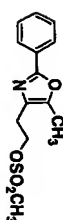


A mixture of Part A compound (18 mg; 0.038 mmol) in concentrated HCl/glacial HOAc (2 mL of a 1:4 solution) was stirred at 70°C for 16 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for the purification of Part F compound) and lyophilized from dioxane to give the title compound (17 mg; 97%) as a white solid.  $[M + H]^+ = 466.2$

#### Example 47

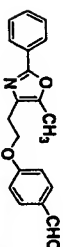


A.



To a -5°C solution of 5-phenyl-2-methyl-oxazole-4-ethanol (20.0 g, 0.098 mol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added methanesulfonyl chloride (12.40 g, 0.108 mol) in one portion (exothermic reaction). After recooling to -5°C,  $\text{Et}_3\text{N}$  (11.1 g, 0.110 mol) was added slowly over 30 min (internal temperature <3°C). The reaction was allowed to warm to RT and stirred for 1 h (reaction monitored by analytical HPLC), at which point starting material had been consumed. The reaction was washed with aqueous HCl (2 x 50 mL of a 3N solution). The combined aqueous layers were extracted with  $\text{CH}_2\text{Cl}_2$  (50 mL). The combined organic extracts were successively washed with satd. aqueous  $\text{NaHCO}_3$  and brine (50 mL each), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated to ~30 mL volume. Methyl tert-butyl ether (120 mL) was added and the mixture was stirred; a white solid was formed. The mixture was cooled to -20°C for complete crystallization. The product was filtered and vacuum-dried to give the product mesylate (23.3 g, 85%) as a white solid. The mother liquor was concentrated in vacuo and recrystallized from methyl tert butyl ether/heptane to give a second crop of product mesylate (3.3 g, 12%; total yield = 97%).

B.

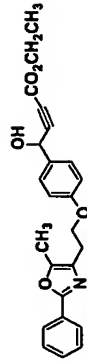


A mixture of Part A compound (13.6 g, 0.048 mol), 4-hydroxybenzaldehyde (7.09 g, 0.058 mol) and  $\text{K}_2\text{CO}_3$  (9.95 g, 0.072 mol) in DMF (110 mL) was heated at 100°C for 2 h (reaction complete by analytical HPLC). The mixture was allowed to cool to RT and then poured into ice-water (400 mL) and stirred for 30 min. The solid product was filtered and washed with cold water (3 x 25 mL) and dried

in vacuo at 50°-60°C overnight. The crude product was crystallized from MTBE-Hexane to give (12.2 g, 82%; 2 crops) Part B compound as a white solid.

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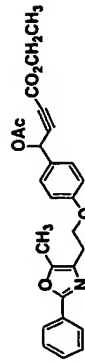
C.



To a RT solution of Part B compound (2.70 g; 8.80 mmol), ethyl trimethylsilylpropionate (2.0 mL; 10.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (40 mL) was added KF (570 mg; 9.8 mmol) and catalytic 18-crown-6 (50 mg; 0.20 mmol). The reaction mixture was stirred at 45°C for 18 h, at which point the reaction was complete by analytical HPLC. The reaction was extracted with aqueous 1 N HCl, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. MeOH (50 mL) and TFA (2 mL) were added and the mixture was stirred at RT for 4 h, then concentrated in vacuo and partitioned between  $\text{Et}_2\text{O}$  and saturated aqueous  $\text{NaHCO}_3$ . The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give Part C compound (3.50 g; 90%) which was used in the next step without further purification.

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D.



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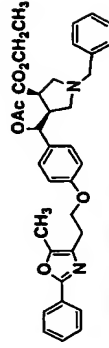
To a 0°C solution of Part C compound (3.50 g; 8.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) were successively added pyridine (1.0 mL; 12.3 mmol) and acetyl chloride (0.8 mL; 11.2 mmol). The reaction was stirred at 0°C for 30 min, then extracted with aqueous 10% HCl and saturated aqueous

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$\text{NaHCO}_3$ . The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give Part D compound (4.0 g; 98%) as an oil which was used in the next step without further purification.

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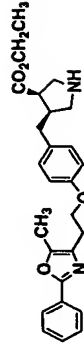
E.



To a RT solution of Part D compound (4.0 g; 8.9 mmol) and Example 1 Part B compound (3.0 g; 12.6 mmol) in toluene (15 mL) was slowly added TFA (100  $\mu\text{L}$ ). An exothermic reaction ensued, and the reaction was stirred at RT for 3 h, then was concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 100% hex to 100%  $\text{EtOAc}$ ) to give Part E compound (2.5 g; 48%) as an oil.

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F.



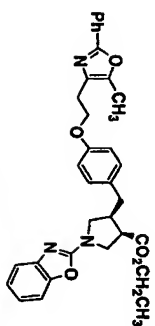
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A mixture of Part E compound (2.50 g; 4.3 mmol) and 10% Pd/C (500 mg) in glacial HOAc (20 mL) was stirred under an atmosphere of  $\text{H}_2$  (65 psi) in a pressurized vessel for 48 h. The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was partitioned between  $\text{EtOAc}$  and saturated aqueous  $\text{NaHCO}_3$ . The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give Part F compound (1.70 g; 90%; acetic acid salt) as an oil.

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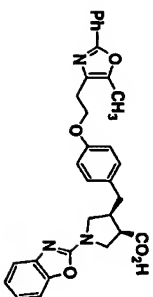
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G.



A mixture of Part F compound (25 mg; 0.057 mmol), 2-chlorobenzoxazole (10 mg; 0.065 mmol) and Et<sub>3</sub>N (20  $\mu$ L; 0.14 mmol) in toluene (1 mL) was stirred at 120°C in a sealed tube for 3 h, then was cooled to RT and concentrated in vacuo. The residue was partitioned between Et<sub>2</sub>O and saturated aqueous NaHCO<sub>3</sub>; the organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to give Part G compound (20 mg; 63%) as an oil.

15 H.



A mixture of Part G compound (10 mg; 0.018 mmol) in glacial HOAc (1 mL) and 20% aqueous HCl (0.25 mL) was heated at 80°C for 18 h, then was cooled to RT and concentrated in vacuo. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NH<sub>4</sub>Cl. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for the purification of Example 26) and lyophilized from H<sub>2</sub>O to give the title compound (5 mg; 55%) as a white solid.

[M + H]<sup>+</sup> = 524.6

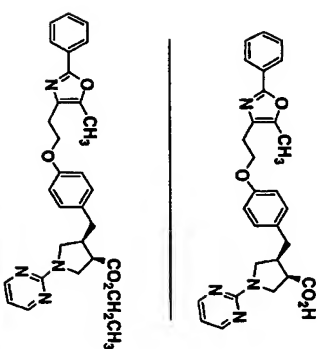
- 194 -

<sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.85 (m, 2 H), 7.37 (m, 4 H), 7.20 (m, 2 H), 7.07 (m, 3 H), 6.79 (d, J = 8.8 Hz, 2 H), 4.12 (t, J = 6.4 Hz, 2 H), 3.95 (m, 1 H), 3.80 (m, 1 H), 3.55 (m, 1 H), 3.45 (m, 1 H), 3.30 (m, 1 H), 2.87 (m, 4 H), 2.45 (m, 1 H).

#### Example 48

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A.

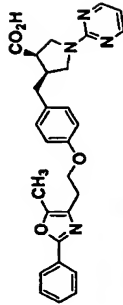


A mixture of Example 47 Part F compound (17 mg; 0.039 mmol) and 2-chloro-pyrimidine (25 mg; 0.22 mmol) and Et<sub>3</sub>N (30  $\mu$ L; 0.22 mmol) was heated in a sealed tube at 130°C for 3 h, then was cooled to RT and concentrated in vacuo. The residue was partitioned between Et<sub>2</sub>O and saturated aqueous NaHCO<sub>3</sub> (20 mL each). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give crude Part A compound, which was used in the next step without further purification.

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- 195 -

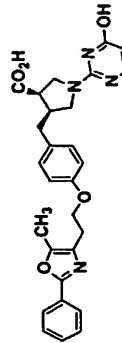
B.



A mixture of crude Part A compound in glacial HOAc (1 mL) and 20% aqueous HCl (0.25 mL) was stirred at 85°C for 18 h, then was cooled to RT and concentrated in vacuo. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and saturated aqueous NH<sub>4</sub>Cl. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for the purification of Example 1 except that an 8 min gradient was employed instead of a 10 min gradient) and lyophilized from H<sub>2</sub>O to give the title compound (10 mg; 50%) as a brown solid.

[M + H]<sup>+</sup> = 485.2

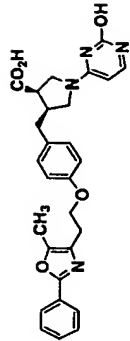
#### Example 49



The title compound (1.2 mg; 4%) was prepared from Example 47 Part F compound (25 mg; 0.058 mmol) and 2,4-dichloro-pyrimidine (10 mg; 0.067 mmol) using the same procedure as for the preparation of Example 48.

[M + H]<sup>+</sup> = 501.2

Also recovered was 0.8 mg (3%) of the regioisomeric product Example 49A compound

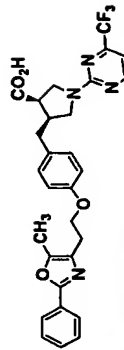


Example 49A compound

[M + H]<sup>+</sup> = 501.2

5

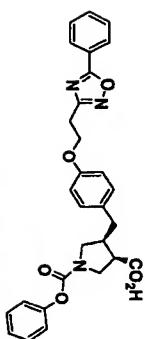
#### Example 50



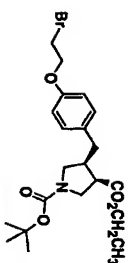
The title compound (15 mg; 50%) was prepared from Example 47 Part F compound (25 mg; 0.057 mmol) and 2-chloro-4-trifluoromethyl-pyrimidine (10 mg; 0.054 mmol) using the same sequence as described for the synthesis of Example 48.

[M + H]<sup>+</sup> = 553.2

15

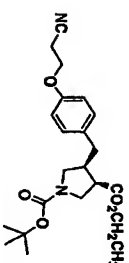
Example 51

5 A.



A mixture of Example 23 Part B compound (1.05 g; 3.0 mmol),  $K_2CO_3$  (1.66 g; 12 mmol) and 1,2-dibromoethane (2.6 mL; 30 mmol) in MeCN (25 mL) was heated at reflux for 40 h. Two additional portions of  $K_2CO_3$  (1.5 g at 12 and 36 h) were added during this time. The reaction was cooled to RT and filtered; the filtrate was concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; stepwise gradient from 9:1 to 3:1 hex:EtOAc) to give Part A compound (1.05 g; 76%) as a syrup.

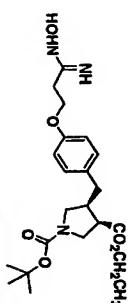
B.



A mixture of Part A compound (1.04 g; 2.3 mmol) and tetrabutylammonium cyanide (1.23 g; 4.6 mmol) in  $CH_2Cl_2$  (10 mL) was stirred at RT for 64 h, then was concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; stepwise gradient from 9:1 to 7:3 hex:EtOAc) to give Part B compound (860 mg; 94%) as a syrup.  $[M + H]^+ = 403.4$

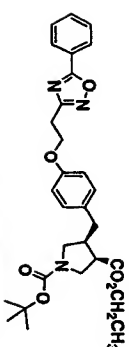
- 198 -

C.



A mixture of Part B compound (160 mg; 0.40 mmol), aqueous  $NH_4OH$  (105 mg of a 50% solution) in MeOH (4 mL) and  $H_2O$  (2 mL) was stirred at 95°C for 3 h, then was cooled to RT and concentrated in vacuo. The residue was partitioned between  $H_2O$  and EtOAc; the organic phase was dried ( $MgSO_4$ ) and concentrated in vacuo to give crude Part C compound (165 mg; 95%) as a white solid, which was used in the next step without further purification.  $[M + H]^+ = 436.4$

15 D.

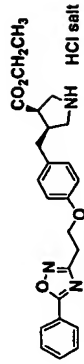


A mixture of Part C compound (95 mg; 0.22 mmol) and benzoyl chloride (30  $\mu$ L; 0.26 mmol) in pyridine (5 mL) was stirred at 130°C for 4 h, then was cooled to RT and concentrated in vacuo. The residue was partitioned between EtOAc and aqueous 1 M HCl (4 mL each); the organic phase was washed with brine (4 mL), dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; stepwise gradient from 9:1 to 4:1 hex:EtOAc) to give Part D compound (85 mg; 75%) as a syrup.  $[M + H]^+ = 522.4$

- 199 -



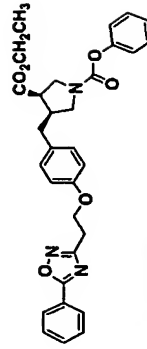
E.



A mixture of Part D compound (85 mg; 0.16 mmol) in  
 5 HCl/dioxane (0.6 mL of a 4 M solution; 2.4 mmol) and  
 $\text{CH}_2\text{Cl}_2$  (3 mL) was stirred at RT for 2 h, then was  
 concentrated in vacuo to give Part E compound (75 mg;  
 100%) as a white solid, which was used in the next step  
 without further purification.

10

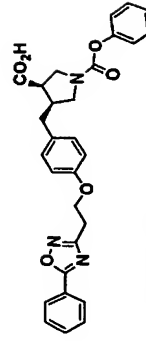
F.



A mixture of Part E compound (25 mg; 0.055 mmol),  
 15 phenyl chloroformate (8  $\mu\text{L}$ ; 0.11 mmol) and  $\text{NaHCO}_3$  (23 mg;  
 0.28 mmol) in THF/ $\text{H}_2\text{O}$  (2 mL of a 1:1 solution) was  
 stirred at RT for 1 h, then was partitioned between EtOAc  
 and  $\text{H}_2\text{O}$  (4 mL each). The organic phase was dried ( $\text{MgSO}_4$ )  
 and concentrated in vacuo. The residue was purified by  
 20 preparative HPLC (as described for the purification of  
 Example 26) to give Part F compound (21 mg; 71%) as a  
 solid.

25

G.



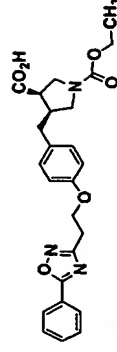
- 200 -

A mixture of Part F compound (21 mg; 0.039 mmol)  
 in concentrated HCl/glacial HOAc (2.4 mL of a 1:5  
 solution) was stirred at 70°C for 16 h, then was cooled  
 to RT and concentrated in vacuo. The residue was  
 5 purified by preparative HPLC (as described for the  
 purification of Part F compound) and lyophilized from  
 dioxane to give the title compound (14 mg; 70%) as a  
 white solid.

$[\text{M} + \text{H}]^+ = 514.2$

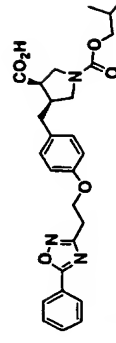
10

### Example 52



The 2-step sequence used to synthesize Example 51  
 from Example 51 Part E compound was also used to prepare  
 the title compound (15 mg; 59% for 2 steps) from Example  
 51 Part E compound (25 mg; 0.055 mmol) and ethyl  
 chloroformate (6  $\mu\text{L}$ ; 0.066 mmol).  
 20  $[\text{M} + \text{H}]^+ = 466.2$

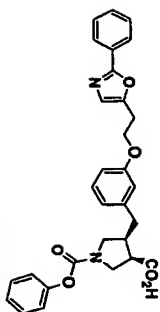
### Example 53



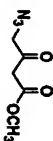
The 2-step sequence used to synthesize Example 51  
 from Example 51 Part E compound was also used to prepare  
 the title compound (15 mg; 52% for 2 steps) from Example  
 51 Part E compound (25 mg; 0.055 mmol) and isobutyl  
 chloroformate (9  $\mu\text{L}$ ; 0.066 mmol).  
 30

- 201 -

$$[M + H]^+ = 494.2$$

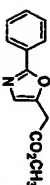
Example 54

A.



- 10 A mixture of methyl 4-chloroacetate (400 mg; 2.6 mmol) and sodium azide (136 mg; 2.1 mmol) in acetone (6 mL) was diluted with H<sub>2</sub>O (~1 mL) until the azide had dissolved. The mixture was heated at 50°C for 1 h, stirred overnight at RT, then was heated at 50°C for 2 h.
- 15 The reaction was cooled to RT and the acetone was removed in vacuo. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>; the combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 3:2 hex:EtOAc) to give Part A compound (237 mgs; 72%).

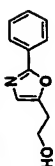
B.



- 25 A mixture of Part A compound (237 mg; 1.51 mmol) and resin-bound Ph<sub>3</sub>P (1.56 g of 3 mmol/g resin; 4.68 mmol) in dioxane (5 mL) was shaken for 10 min at RT. Benzoyl chloride (263 mg; 1.87 mmol) was then added and the reaction was heated at 75°C for 2 h, then cooled to RT and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed (SiO<sub>2</sub>; continuous

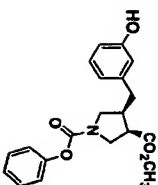
gradient from 100% hex to 1:1 hex:EtOAc; compound was pre-loaded onto the column with Celite®) to give Part B compound (95 mg; 28%) as a pale yellow oil.

C.



- 5 A solution of LiAlH<sub>4</sub> in THF (2.0 mL of a 1 M solution; 2.0 mmol) was added dropwise to Part B compound (95 mg; 0.44 mol) at RT. The reaction was stirred overnight at RT, then was cooled to 0°C and quenched cautiously with H<sub>2</sub>O. Aqueous 3 N NaOH was added and the mixture was concentrated in vacuo. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>; the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc; compound preloaded onto column with CH<sub>2</sub>Cl<sub>2</sub>) to provide Part C compound (100 mg; 100%) as a colorless oil.

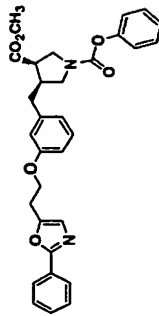
D.



- 25 A RT mixture of Example 32 Part F compound (100 mg; 0.298 mmol) and 4 M HCl/dioxane (1 mL; 4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at RT for 2 h, then was concentrated in vacuo. A mixture of the residue (crude pyrrolidine-phenol) and phenyl chloroformate (60 µL; 0.461 mmol) in saturated aqueous NaHCO<sub>3</sub> (1.5 mL) and THF (1 mL) was stirred at RT overnight, after which the THF was removed

in vacuo. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3X). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated in vacuo; the residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 100% hex to 100% EtOAc) to give Part D compound (110 mg; 100%) as a colorless oil.

E.

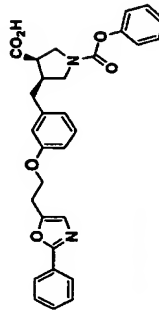


10

A mixture of Part C compound (25 mg; 0.132 mmol), Part D compound (35 mg; 0.098 mmol) and cyanomethylene tributylphosphorane (60  $\mu\text{L}$ ; 0.25 mmol) in toluene (500  $\mu\text{L}$ ) at  $70^\circ\text{C}$  was shaken overnight, then was concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 100% hex to 2:3 hex:EtOAc) to give Part E compound (9 mg; contaminated with 50% Part D compound; 13%) as a yellow oil.  $[\text{M} + \text{H}]^+ = 527.3$

20

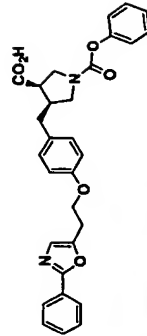
F.



A mixture of Part E compound (4.5 mg; 0.008 mmol) in concentrated HCl (100  $\mu\text{L}$ ) and HOAc (400  $\mu\text{L}$ ) was heated at  $70^\circ\text{C}$  for 24 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as

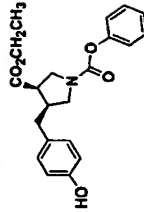
for the purification of Example 26) to give the title compound (2 mg; 40%) as a solid.  $[\text{M} + \text{H}]^+ = 513.1$

5

Example 55

A.

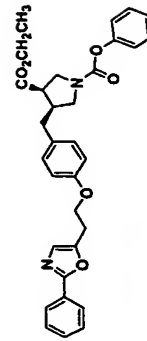
10



A RT mixture of Example 23 Part E compound (100 mg; 0.271 mmol) and 4 M HCl/dioxane (1 mL; 4 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was stirred at RT for 2 h, then was concentrated in vacuo. A mixture of the residue (crude pyrrolidine-phenol) and phenyl chloroformate (60  $\mu\text{L}$ ) in saturated aqueous  $\text{NaHCO}_3$  (1.5 mL) and THF (1 mL) was stirred at RT overnight, then the THF was removed in vacuo. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3X). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated in vacuo; the residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 100% hex to 100% EtOAc) to give Part A compound (65 mg; 62%) as a colorless oil.

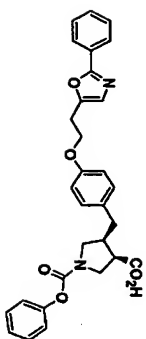
25

B.



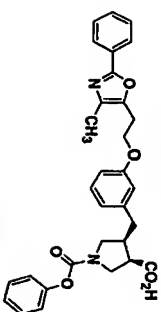
A mixture of Example 54 Part C compound (25 mg; 0.132 mmol), Part A compound (35 mg; 0.095 mmol) and cyanomethylene tributylphosphorane (60  $\mu$ L; 0.248 mmol) in toluene (500  $\mu$ L) at 70°C was shaken overnight, then was concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 100% hex to 2:3 hex:EtOAc) to give Part B compound (30 mg; contaminated with 50% Part A compound; 43%) as a yellow oil.  $[M + H]^+ = 541.4$

## C.

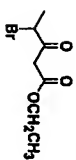


A mixture of Part B compound (15 mg; 0.027 mmol) in concentrated HCl (100  $\mu$ L) and HOAc (400  $\mu$ L) was stirred at 70°C for 24 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as for the purification of Example 26) to give the title compound (3 mg; 20%) as a solid.  $[M + H]^+ = 513.1$

## Example 56



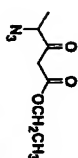
## A.



To a 0°C solution of ethyl propionylacetate (10.0 g, 69.4 mmol) in  $\text{CHCl}_3$  (60 mL) was added dropwise a solution

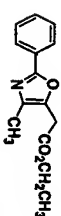
of Br<sub>2</sub> (3.6 mL; 69.4 mmol) in  $\text{CHCl}_3$  (20 mL) and the resulting mixture was stirred at 0°C for 0.5 h. The reaction was allowed to warm to RT and stirred at RT for 0.5 h. Air was then bubbled into the mixture for 1 h. Volatiles were then removed in vacuo to yield an oily residue to provide crude Part A compound (15.3 g, >95% yield) as an oil which was used in the next reaction without further purification.

## B.



A mixture of Part A compound (400 mg; 1.79 mmol) and sodium azide (136 mg; 2.09 mmol) in acetone (6 mL) and  $\text{H}_2\text{O}$  (1 mL) was stirred at RT for 1 h, then at 50°C for 1 h. Analytical HPLC indicated that the starting material had been consumed at this point. The acetone was removed in vacuo and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated in vacuo; the residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 100% hex to 1:1 hex:EtOAc) to give Part B compound (280 mg; 85%) as a pale yellow oil.

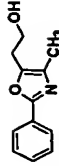
## C.



A mixture of Part B compound (100 mg; 0.54 mmol) and resin-bound Ph<sub>3</sub>P (540 mg of 3 mmol/g resin; 1.62 mmol) in dioxane (4 mL) was shaken for 10 min at RT. Benzoyl chloride (84 mg; 0.60 mmol) was then added and the reaction was heated at 75°C for 2 h, then cooled to RT and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed ( $\text{SiO}_2$ ; continuous

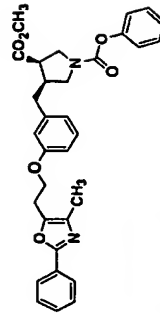
gradient from 100% hex to 1:1 hex:EtOAc; the compound was pre-loaded onto the column with Celite®) to give Part C compound (280 mg; 85%) as a pale yellow oil.

5 D.



A solution of LiAlH<sub>4</sub> in THF (1 mL of a 1 M solution; 10 1 mmol) was added dropwise to Part C compound (75 mg; 0.30 mol) at 0°C. The reaction was warmed to RT and stirred overnight at RT, then was cooled to 0°C and quenched cautiously with H<sub>2</sub>O. Aqueous 3 N NaOH was added and the mixture was concentrated in vacuo. The residue 15 was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>; the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc; compound preloaded onto 20 column with CH<sub>2</sub>Cl<sub>2</sub>) to provide Part D compound (55 mg; 89%) as a colorless oil.

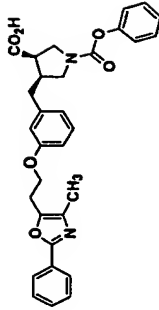
E.



A mixture of Part D compound (25 mg; 0.123 mmol), 25 Example 54 Part D compound (35 mg; 0.098 mmol) and cyanomethylene tributylphosphorane (60 µL; 0.248 mmol) in toluene (500 µL) at 70°C was shaken overnight, then was 30 concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 2:3 hex:EtOAc) to give Part E compound (33 mg; contaminated

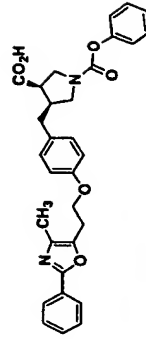
with 10% Example 54 Part D compound; 60%) as a yellow oil.  
[M + H]<sup>+</sup> = 541.4

5 F.



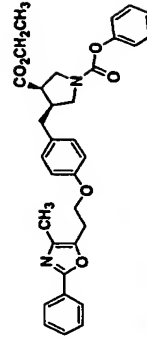
A mixture of Part E compound (16 mg; 0.031 mmol) in 10 concentrated HCl (100 µL) and acetic acid (400 µL) was heated at 70°C for 24 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as for the purification of Example 26) to give the title compound (7.5 mg; 45%) as a solid. 15 [M + H]<sup>+</sup> = 527.1

#### Example 57



20

A.

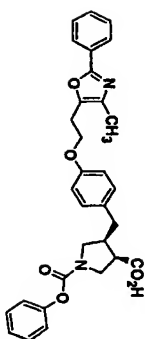


25

A mixture of Example 56 Part D compound (25 mg; 0.123 mmol), Example 55 Part A compound (35 mg; 0.095 mmol) and cyanomethylene tributylphosphorane (60  $\mu$ L; 0.248 mmol) in toluene (500  $\mu$ L) at 70°C was shaken overnight, then was concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 100% hex to 2:3 hex:EtOAc) to give Part A compound (27 mg; contaminated with 12% Example 56 Part D compound; 43%) as a yellow oil.

[M + H]<sup>+</sup> = 555.4

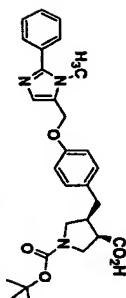
## B.



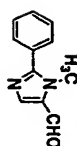
A mixture of Part A compound (13 mg; 0.024 mmol) in concentrated HCl (100  $\mu$ L) and HOAc (400  $\mu$ L) was heated at 70°C for 24 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as for the purification of Example 26) to give the title compound (7.5 mg; 60%) as a solid.

[M + H]<sup>+</sup> = 527.1

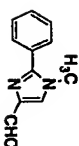
## Example 58



## A.

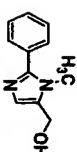


To a solution of 4-formyl-2-phenylimidazole (100 mg, 0.58 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added aqueous KOH (2 mL of a 30% solution), followed by dimethyl sulfate (66  $\mu$ L, 0.70 mmol), and tetrabutylammonium bromide (10 mg; 0.039 mmol). The reaction mixture was stirred overnight at RT and then was partitioned between EtOAc and water; the organic phase was washed with brine and then concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 1:1 hexane:EtOAc to 100% EtOAc) to give 1-methyl-2-phenyl-imidazole-5-carboxaldehyde as a solid (35 mg; 32%; 1<sup>st</sup> eluted fraction; Part A compound) and Part B compound



(45 mg; 42%; second eluted fraction) as a solid.

## C.

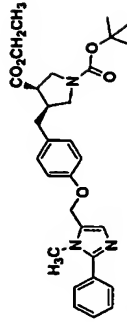


To a solution of Part A compound (50 mg, 0.27 mmol) in MeOH (2 mL) was added  $\text{NaBH}_4$  (30 mg; 0.79 mmol). The

mixture was stirred at RT for 1 h, after which the reaction was quenched with excess saturated aqueous  $\text{NH}_4\text{Cl}$  (1 mL). Volatiles were removed in vacuo, and the residue was partitioned between saturated aqueous  $\text{NaHCO}_3$  and EtOAc. The organic phase was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give Part C compound as a white solid (37 mg, 75%).

5 In addition, the epimerized compound, Example 59, was also obtained (5 mg; 17%) as a solid.

D.

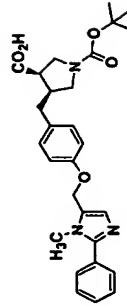


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A mixture of Example 23 Part E compound (50 mg; 0.14 mmol), Part C compound (40 mg; 0.21 mmol) and cyanomethylene tributylphosphorane (50 mg; 0.21 mmol) in toluene (1.5 mL) was stirred at  $88^\circ\text{C}$  for 3 h, then was cooled to RT and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 3:2 to 1:4 hex:EtOAc) to give Part D compound (30 mg; 40%) as an oil.

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E.



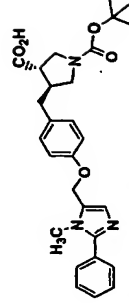
A mixture of Part D compound (30 mg; 0.057 mmol) and  $\text{LiOH}\cdot\text{H}_2\text{O}$  (30 mg; 0.71 mmol) in MeOH (0.3 mL), THF (1 mL) and  $\text{H}_2\text{O}$  (0.5 mL) was stirred at RT for 1 h, after which saturated aqueous  $\text{NH}_4\text{Cl}$  (1 mL) was added. Volatiles were removed in vacuo and the residue was partitioned between EtOAc and  $\text{H}_2\text{O}$ . The aqueous phase was extracted with EtOAc; the combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The residue was purified by

preparative HPLC (as for the purification of Example 26 except that a continuous gradient from 40:60 A:B to 100% B was used) to give the title compound (5 mg; 17%) as a solid.

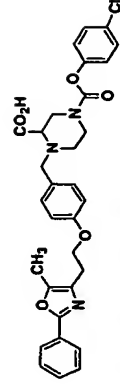
5  $[\text{M} + \text{H}]^+ = 527.1$

In addition, the epimerized compound, Example 59, was also obtained (5 mg; 17%) as a solid.

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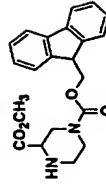
Example 59

15  $[\text{M} + \text{H}]^+ = 527.1$

Example 60

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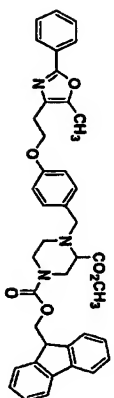
A.



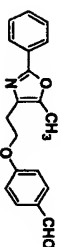
HCl gas was bubbled through a solution of N-1-Boc-N-4-Fmoc-2-piperazine carboxylic acid (5.0 g; 11 mmol) in MeOH (250 mL) at RT for 5 min. The reaction was stirred at RT for 5 h, then was concentrated in vacuo. The residue was partitioned between EtOAc and 1N aqueous NaOH. The organic phase was dried ( $\text{MgSO}_4$ ) and

concentrated in vacuo to give Part A compound (3.8 g; 95%) as an oil.

B.

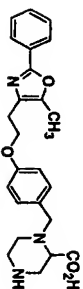


To a RT solution of Part A compound (1.0 g; 2.7 mmol) and the aldehyde Example 47 Part B compound (840 mg; 2.7 mmol)



in  $\text{CH}_2\text{Cl}_2$  (150 mL) were successively added HOAc (1 mL) and  $\text{NaBH}(\text{OAc})_3$  (930 mg; 4.7 mmol). The reaction was stirred at RT for 1 h and then washed with saturated aqueous  $\text{NaHCO}_3$ . The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to furnish Part B compound (1.74 g; 97%) as an oil.

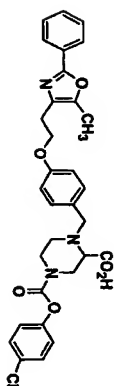
C.



A solution of Part B compound (1.74 g; 2.65 mmol) and KOH (740 mg; 13.2 mmol) in  $\text{MeOH}/\text{H}_2\text{O}$  (40 mL of a 1:1 solution) was stirred at RT for 18 h. Volatiles were removed in vacuo, and the residue was purified by preparative HPLC (YMC reverse-phase ODS 30 x 250 mm column; detection at 220 nm; flow rate = 25 mL/min; continuous gradient from 100% A to 100% B over 30 min + 10 min hold time at 100% B, where A = 90:10:0.1

$\text{H}_2\text{O}:\text{MeOH}:\text{TFA}$  and B = 90:10:0.1  $\text{MeOH}:\text{H}_2\text{O}:\text{TFA}$ ) to provide Part C compound (510 mg; 40%) as an oil.

D.



To a RT solution of Part C compound (50 mg; 0.11 mmol) and 4-chlorophenyl chloroformate (28 mg; 0.14 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added  $\text{Et}_3\text{N}$  (70  $\mu\text{L}$ ; 0.52 mmol). The reaction was stirred at RT for 16 h and then was concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 100% A to 100% B over 30 min + 10 min hold time at 100% B, where A = 90:10:0.1  $\text{H}_2\text{O}:\text{MeOH}:\text{TFA}$  and B = 90:10:0.1  $\text{MeOH}:\text{H}_2\text{O}:\text{TFA}$ ) to provide the title compound (28 mg; 44%) as a solid.  $[\text{M} + \text{H}]^+ = 577.2$

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#### Examples 61-71

Examples 61 through 71 were prepared in a similar fashion to Example 60 (from Example 60 Part C compound) using a variety of chloroformates.

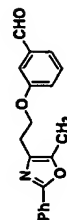
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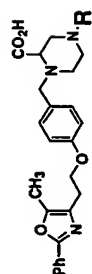
Example #	R	[M + H] <sup>+</sup>
69		577.4
70		572.2
71		592.2

Examples 72-73

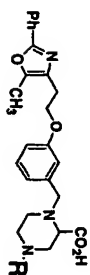
Examples 72 and 73 were prepared using an analogous synthetic sequence to that used for the synthesis of Example 60. The only difference was that the aldehyde used was Example 436 Part A compound



instead of the aldehyde in Example 60.



Example #	R	[M + H] <sup>+</sup>
61		542.1
62		572.3
63		577.4
64		618.1; 620.1
65		560.2
66		556.2
67		600.2
68		610.2



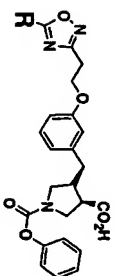
Example #	R	[M+H] <sup>+</sup>
72		542.4
73		572.2

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Examples 74-88

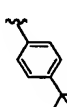
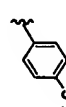
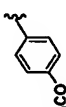
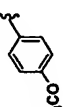
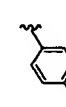
Following the general sequence for the preparation of Example 45 compound (using appropriately substituted benzoyl chlorides instead of benzoyl chloride), the following compounds of the invention were prepared from Example 45 Part C compound.

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Example No.	R	[M+H] <sup>+</sup>
74		528.4

Example No.	R	[M+H] <sup>+</sup>
75		582.4
76		544.4
77		528.5
78		582.4
79		598.4
80		544.4
81		558.4
82		550.4
83		528.5

Example No.	R	[M+H] <sup>+</sup>
84		570.5
85		582.4
86		598.4
87		544.4
88		548.4

butanedione mono-oxime (25.0 g, 234 mmol) in one portion and the resulting solution was stirred at RT for 12 h. Analytical HPLC indicated that all starting materials had been consumed. The reaction mixture was concentrated in vacuo to yield Part A compound as a white solid, which was used in the next step without further purification.

B.

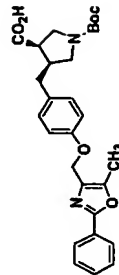


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To a solution of Part A compound in CHCl<sub>3</sub> (200 mL) was added dropwise POCl<sub>3</sub> (30 mL, 320 mmol). The reaction was stirred for 12 h at 50°C, then was concentrated in vacuo. The brown residue was partitioned between EtOAc (300 mL) and 1N aqueous NaOH. The organic phase was washed with brine, dried, (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; Et<sub>2</sub>O) to give Part B compound (41.5 g; 86%) as a light brown solid (>95% pure by analytical HPLC and <sup>1</sup>H-NMR analysis).

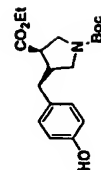
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C.



A mixture of Example 23 Part E compound (140 mg; 0.4 mmol),

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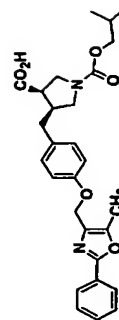


A.

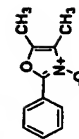
Part B compound (124 mg; 0.6 mmol) and K<sub>2</sub>CO<sub>3</sub> (83 mg; 0.6 mmol) in CH<sub>3</sub>CN (10 mL) was stirred at 95°C for 2h. The solids were filtered off, and the filtrate was

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### Example 89



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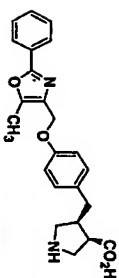


To a solution of benzaldehyde (23.8 g, 234 mmol) in EtOAc (150 mL; pre-saturated with HCl gas) was added 2,3-

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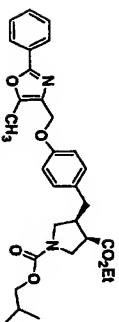
concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 9:1 to 4:1 hex:EtOAc) to give Part C compound (180 mg; 86%) as an oil.

D.



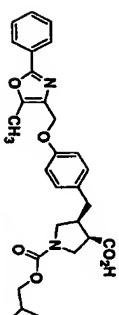
To a solution of Part C compound (180 mg; 0.35 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added HCl in dioxane (0.5 mL of a 4M solution; 2 mmol). The reaction was stirred at RT for 2 h, then was concentrated in vacuo to give crude Part D compound (152 mg; 96%) as a white solid, which was used in the next reaction without further purification.

E.



A solution of Part D compound (25 mg; 0.055 mmol), isobutyl chloroformate (11  $\mu$ L; 0.083 mmol) and NaHCO<sub>3</sub> (18 mg; 0.22 mmol) in 1:1 THF:H<sub>2</sub>O (3 mL) was stirred at RT for 30 min, then was partitioned between EtOAc and H<sub>2</sub>O. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 50% A to 100% B over 10 min + 3 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give Part E compound (20 mg; 70%) as an oil.

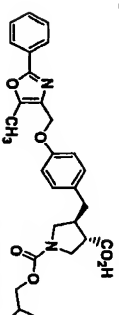
F.



A solution of Part E compound (20 mg; 0.04 mmol) and LiOH (6 mg; 0.16 mmol) in THF/H<sub>2</sub>O (2 mL of a 1:1 solution) was stirred at RT for 18 h. The reaction was acidified to pH 3 with 1 M aqueous HCl and extracted with EtOAc (2x). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 50% A to 100% B over 10 min + 3 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give the title compound as a white solid (7.3 mg; 39%). [M + H]<sup>+</sup> = 493.5

In addition, a second fraction from the preparative HPLC of the above crude product was identified as the epimerized trans-isomer Example 90 compound (white solid; 3.6 mg; 19%).

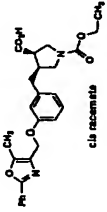
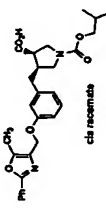
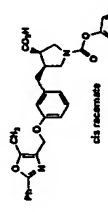
[M + H]<sup>+</sup> = 493.5



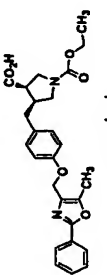
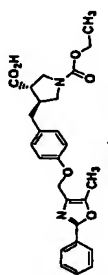
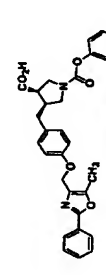
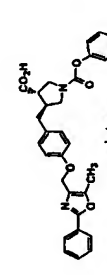
#### Examples 91-94

Following the general procedure for the synthesis of Examples 89 and 90, the following compounds [Examples 91-94] of the invention were prepared:

was used instead of Example 23 Part E compound (the ethyl ester), the following compounds of the invention were prepared:

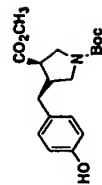
Example No.	Structure	[M+H] <sup>+</sup>
95	 cis racemate	465.5
96	 cis racemate	493.5
97	 cis racemate	513.5

5

Example No.	Structure	[M+H] <sup>+</sup>
91	 racemic cis	465.5
92	 racemic trans	465.5
93	 racemic cis	513.5
94	 racemic trans	513.5

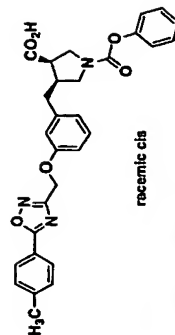
Examples 95-97

5 Following the general procedure for the synthesis of Example 89, except that Example 32 Part F compound (the methyl ester)



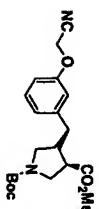
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Example 98

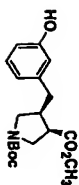


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A.

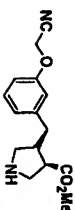


A mixture of Example 32 Part F compound (600 mg; 1.8 mmol),  $K_2CO_3$  (1.2; 9.0 mmol)



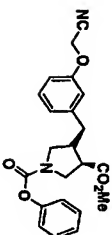
and  $\alpha$ -chloroacetonitrile (0.6 mL; 9.0 mmol) in  $CH_3CN$  (10 mL) was heated at  $95^\circ C$  for 3 h. Solids were filtered off, and the filtrate was concentrated in vacuo. The residue was chromatographed ( $SiO_2$ , 4:1 to 7:3 hex:EtOAc) to give Part A compound as an oil (554 mg; 83%).

15 B.



To a solution of Part A compound (554 mg; 1.5 mmol) in  $CH_2Cl_2$  (5 mL) was added HCl in dioxane (1 mL of a 4 M solution; 4 mmol). The reaction mixture was stirred at RT for 3 h. Volatiles were removed in vacuo to give crude Part B compound (425 mg; 92% yield) as a white solid, which was used in the next reaction without further purification.

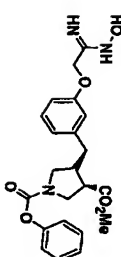
25 C.



A solution of Part B compound (425 mg; 1.4 mmol), phenyl chloroformate (205  $\mu$ L; 1.7 mmol) and  $NaHCO_3$  (470

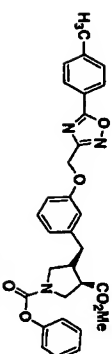
mg; 5.6 mmol) in THF/ $H_2O$  (10 mL of a 1:1 solution) was stirred at RT for 1h, then was partitioned between EtOAc and  $H_2O$ . The organic phase was washed with brine, dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ , 4:1 to 7:3 hex:EtOAc) to give Part C compound as an oil (500 mg; 93%).

D.



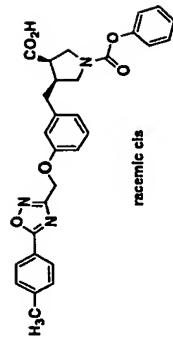
A solution of Part C compound (500 mg; 1.3 mmol), and  $NH_4OH$  (420 mg; 3.3 mmol) in MeOH (10 mL) and  $H_2O$  (5 mL) was stirred at  $95^\circ C$  for 3 h. Volatiles were removed in vacuo, and the residue was lyophilized from dioxane to give Part D compound (493 mg; 91%) as a solid, which was used in the next reaction without further purification.

E.



To a solution of Part D compound (25 mg; 0.06 mmol) in pyridine (1 mL) was added p-methyl benzoyl chloride (9  $\mu$ L; 0.07 mmol). The reaction was stirred at  $115^\circ C$  for 4 h, then was cooled to RT and concentrated in vacuo to give crude Part E compound, which was used in the next step without further purification.

F.



5

A solution of crude Part E compound and LiOH (9 mg; 0.2 mmol) in THF/H<sub>2</sub>O (2 mL of a 1:1 solution) was stirred at RT for 18 h, then was acidified to pH 3 with excess 1M aqueous HCl. The aqueous phase was extracted with EtOAc (2x). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 50% A to 100% B over 10 min + 3 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give the title compound as a white solid (8.5 mg; 28% yield for 2 steps).

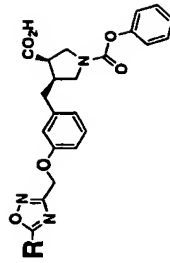
[M + H]<sup>+</sup> = 514.6

20

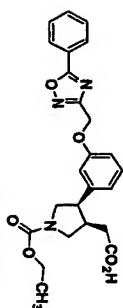
#### Examples 99-105

Following the general procedure for the synthesis of Example 98, the following compounds of the invention were prepared.

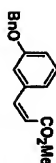
25



Example No.	R	[M+H] <sup>+</sup>
99		530.6
100		544.5
101		556.6
102		558.6
103		584.5
104		584.5
105		530.6

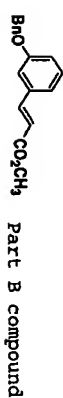
Example 106

5 A.



To a  $-78^{\circ}\text{C}$  solution of methyl bis(trifluoroethyl) phosphonoacetate (1.3 g; 4.1 mmol) in dry THF (10 mL) under Ar was added NaH (141 mg of a 60% dispersion in mineral oil; 3.6 mmol) in one portion, and the mixture was stirred at  $-78^{\circ}\text{C}$  for 30 min. A solution of 3-benzyloxy-benzaldehyde (500 mg; 2.4 mmol) in dry THF (5 mL) was then added dropwise and the reaction was stirred for 3h at  $-78^{\circ}\text{C}$ . The reaction was then quenched by dropwise addition of saturated aqueous  $\text{NH}_4\text{Cl}$ , warmed to RT and partitioned between EtOAc and  $\text{H}_2\text{O}$ . The organic phase was washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; 100% hex to 85:15 hex:EtOAc) to give Part A compound (the desired cis isomer; 470 mg) as an oil.

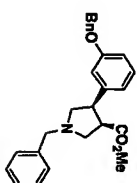
In addition, Part B compound, the trans isomer (60 mg) was also obtained as an oil.



Part B compound

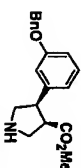
The combined yield of both isomers was 96%.

C.



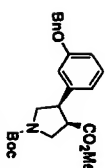
To a solution of Part A compound (470 mg; 1.8 mmol), and Example 1 Part B compound (622 mg; 2.7 mmol) in toluene (15 mL) was added TFA (50  $\mu\text{L}$ ) dropwise. The mixture was stirred at RT for 1 h, then was partitioned between EtOAc and saturated aqueous  $\text{NaHCO}_3$ . The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; 100% hex to 7:3 hex:EtOAc) to give Part C compound (650 mg; 92%) as an oil.

D.



To a  $0^{\circ}\text{C}$  solution of Part C compound (600 mg; 1.5 mmol) in DCE (5 mL) was added dropwise 1-chloroethyl chloroformate (321  $\mu\text{L}$ ; 3.0 mmol) and the reaction mixture was heated at  $60^{\circ}\text{C}$  for 2 h. Volatiles were removed in vacuo, and the residue was dissolved in MeOH (5 mL) and heated at  $60^{\circ}$  for 1 h. Volatiles were removed in vacuo, and the residue was lyophilized (dioxane) to give crude Part D compound (590 mg) as a white solid, which was used in the next step without further purification.

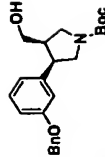
E.





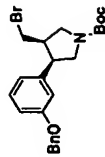
A solution of Part D compound (590 mg; 1.7 mmol), di-tert-butyl dicarbonate (327 mg; 1.5 mmol), and NaHCO<sub>3</sub> (252 mg; 3.0 mmol) in THF/H<sub>2</sub>O (10 mL of a 1:1 solution) was stirred at RT for 1 h, then was partitioned between EtOAc and H<sub>2</sub>O. The organic phase was washed with brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 9:1 to 4:1 hex:EtOAc) to give Part E compound as an oil (530 mg; 86% yield for 2 steps).

10 F.



To a -78°C solution of Part E compound (530 mg; 1.3 mmol) in dry THF (5 mL) was added dropwise LiAlH<sub>4</sub> in THF (1.3 mL of a 1 M solution; 1.3 mmol). The mixture was warmed to 0°C and stirred at 0°C for 30 min, then was cautiously quenched by dropwise addition of EtOAc and saturated aqueous sodium potassium tartrate, and finally partitioned between EtOAc and H<sub>2</sub>O. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 4:1 to 3:2 hex:EtOAc) to give Part F compound (390 mg; 79%) as an oil.

G.

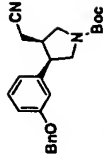


25

To a 0°C solution of Part F compound (250 mg; 0.7 mmol), and Ph<sub>3</sub>P (206 mg; 0.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added dropwise a solution of CBr<sub>4</sub> (323 mg; 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL). The mixture was stirred at RT for 2 h and then heated at reflux for 2 h. After cooling to RT, volatiles were removed in vacuo, and the residue was chromatographed (SiO<sub>2</sub>; 9:1 to 7:3 hex:EtOAc) to give Part G compound (169 mg; 70%).

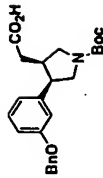
- 232 -

H.



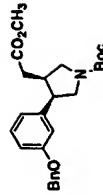
A solution of Part G compound (169 mg; 0.4 mmol) and tetrabutylammonium cyanide (406 mg; 1.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was stirred at RT for 18h, then was heated to reflux for 2 h. Volatiles were removed in vacuo, and the residue was chromatographed (SiO<sub>2</sub>; 9:1 to 7:3 hex:EtOAc) to give Part H compound (45 mg; 65%).

I.



A solution of Part H compound (2.9 g; 7.4 mmol) and 30% aqueous KOH (10 mL) in MeOH (20 mL) was heated at 100°C for 5 h, then was cooled to RT, acidified to pH 5 with aqueous 1M HCl and finally partitioned between EtOAc and H<sub>2</sub>O. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to give crude Part I compound (2.8 g; 93%), which was used in the next reaction without further purification.

J.



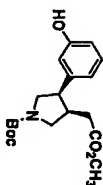
25

To a -78°C solution of Part I compound (2.8 g; 6.9 mmol) in MeOH (30 mL) was added dropwise a solution of TMSCHN<sub>3</sub> in hexane (17.1 mL of a 2 M solution; 34.2 mmol), then was allowed to warm to RT and stirred at RT for 5 h. Volatiles were removed in vacuo, and the residue was

- 233 -

chromatographed (SiO<sub>2</sub>; 100% hex to 3:7 hex:EtOAc) to give Part J compound (2.5 g; 86%) as an oil.

K.

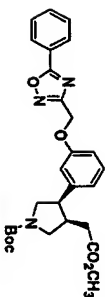


5

A mixture of Part J compound (1.0 g; 2.4 mmol), and 10% Pd/C (80 mg) in MeOH (30 mL) and glacial HOAc (5 drops) was stirred at RT for 4 h under an atmosphere of H<sub>2</sub> (balloon), then was neutralized with excess NaHCO<sub>3</sub> and filtered. The filtrate was concentrated in vacuo to give Part K compound as an oil (730 mg; 93%).

10

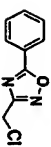
L.



15

A mixture of Part K compound (120 mg; 0.4 mmol), Example 25 Part C compound (116 mg; 0.6 mmol)

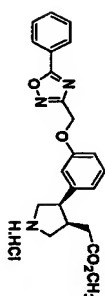
20



and K<sub>2</sub>CO<sub>3</sub> (100 mg; 0.8 mmol) in CH<sub>3</sub>CN (6 mL) was heated at 95°C for 2 h, then was cooled to RT. Solids were filtered off, and the filtrate was concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 95:5 to 85:15 hex:EtOAc) to give Part L compound (160 mg; 91%) as an oil.

25

M.

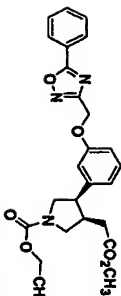


5

A solution of Part L compound (145 mg; 0.3 mmol) and HCl in dioxane (0.5 mL of a 4M solution; 2.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was stirred at RT for 2 h. Volatiles were removed in vacuo to give Part M compound (126 mg; 100%) as a white solid

10

N.

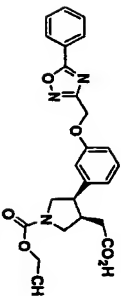


15

A solution of Part M compound (20 mg; 0.05 mmol), ethyl chloroformate (6 µL, 0.07 mmol) and NaHCO<sub>3</sub> (16 mg; 0.2 mmol) in THF/H<sub>2</sub>O (2 mL of a 1:1 solution) was stirred at RT for 1 h, then was partitioned between EtOAc and H<sub>2</sub>O. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part N compound, which was used in the next step without further purification.

20

O.



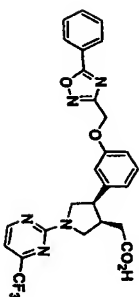
25

A solution of Part N compound and LiOH (10 mg; 0.24 mmol) in THF/H<sub>2</sub>O (2 mL of a 1:1 solution) was stirred at RT for 2 h, then was acidified to pH 2 with aqueous 1 M HCl, and finally partitioned between EtOAc and H<sub>2</sub>O. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC



in vacuo to give crude Part A compound, which was used in the next step without further purification.

B.

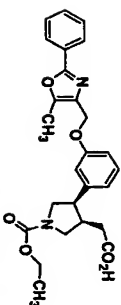


5

A solution of crude Part A compound and LiOH (10 mg; 0.24 mmol) in THF/H<sub>2</sub>O (2 mL of a 1:1 solution) was stirred at RT for 2 h, then was acidified to pH 2 with aqueous 1 M HCl, and finally partitioned between EtOAc and H<sub>2</sub>O. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 50% A to 100% B over 10 min + 4 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) and lyophilized from dioxane to furnish the title compound as a white solid (31 mg; 97%). [M + H]<sup>+</sup> = 526.0

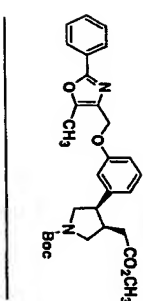
20

### Example 113

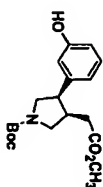


25

A.

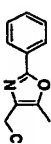


A mixture of Example 106 Part K compound (120 mg; 0.4 mmol),



5

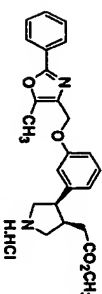
**Example 89 Part B compound (112 mg; 0.6 mmol)**



10 and  $K_2CO_3$  (100 mg; 0.8 mmol) in  $CH_3CN$  (6 mL) was heated at  
95°C for 2 h, then cooled to RT. Solids were filtered  
off, and the filtrate was concentrated in vacuo. The  
residue was chromatographed ( $SiO_2$ ; 95:5 to 85:15  
hex:EtOAc) to give Part A compound (145 mg; 80%) as an  
oil.

15

B.

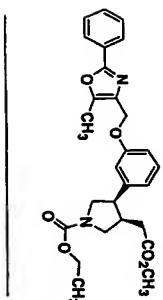


20

20 A solution of Part A compound (133 mg; 0.3 mmol) and  
HCl in dioxane (0.5 mL of a 4M solution; 2.0 mmol) in  
CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was stirred at RT for 2 h, then was  
concentrated in vacuo to give Part B compound as a white  
solid (110 mg; 93%), which was used in the next step  
25 without further purification.

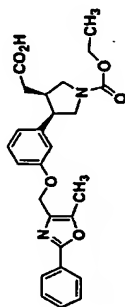
2

3.



A solution of Part B compound (16 mg; 0.04 mmol), 2-ethyl chloroformate (5  $\mu$ L, 0.06 mmol), and  $\text{NaHCO}_3$  (15 mg; 0.2 mmol) in THF/ $\text{H}_2\text{O}$  (2 mL of a 1:1 solution) was stirred at RT for 1 h. Volatiles were removed in vacuo, and the residue was partitioned between EtOAc and  $\text{H}_2\text{O}$ . The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give Part C compound, which was used in the next step without further purification.

10 D.

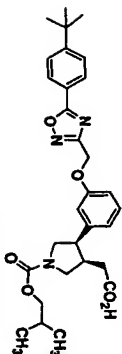


A solution of Part C compound and  $\text{LiOH} \cdot \text{H}_2\text{O}$  (10 mg; 0.24 mmol) in 1:1 THF: $\text{H}_2\text{O}$  (2 mL) was stirred at RT for 2 h, then was acidified to pH 2 with 1 M aqueous HCl, and finally partitioned between EtOAc and  $\text{H}_2\text{O}$ . The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 50% A to 100% B over 10 min + 4 min hold time at 100% B, where A = 90:10:0.1  $\text{H}_2\text{O}$ :MeOH:TFA and B = 90:10:0.1 MeOH: $\text{H}_2\text{O}$ :TFA) and lyophilized from dioxane to furnish the title compound (11 mg; 66%) as a white solid.  $[\text{M} + \text{H}]^+ = 465.5$

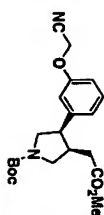
#### Examples 114-118

Following the procedure for the synthesis of Example 113, the following compounds of the invention were prepared.

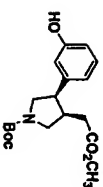
Example No.	R	$[\text{M} + \text{H}]^+$
114		479.6
115		493.6
116		513.6
117		543.6
118		493.6

**Example 119**

5 A.



A solution of Example 106 Part K compound (150 mg; 0.5 mmol)

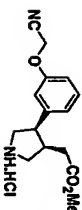


$\alpha$ -Chloroacetonitrile (140  $\mu$ L; 2.5 mmol) and  $K_2CO_3$  (310 mg; 2.5 mmol) in  $CH_3CN$  (15 mL) was heated at 90°C for 2 h.

Solids were filtered off and the filtrate was

concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; 85:15 hex: EtOAc) to give Part A compound (90mg; 54%) as an oil.

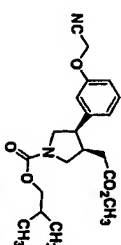
20 B.



A solution of Part A compound (90 mg; 0.2 mmol), and HCl in dioxane (0.5 mL of a 4M solution; 2.0 mmol) in  $CH_2Cl_2$  (4 mL) was stirred at RT for 3 h. Volatiles were removed in vacuo to give Part B compound, which was used in the next step without further purification.

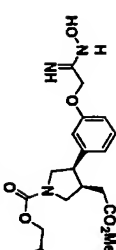
- 242 -

C.



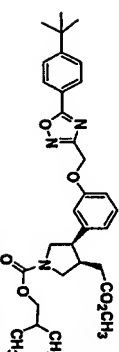
A mixture of Part C compound, isobutyl chloroformate (37  $\mu$ L; 0.3 mmol) and  $NaHCO_3$  (80 mg; 1.0 mmol) in 1:1 THF:H<sub>2</sub>O (4 mL) was stirred at RT for 30 min, then was partitioned between EtOAc and H<sub>2</sub>O. The organic phase was dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; 3:1 hex:EtOAc) to give Part C compound (30 mg; 33%) as an oil.

D.



A solution of Part C compound (90 mg; 0.2 mmol), and 50%  $NH_2OH/H_2O$  (75 mg) in MeOH (6 mL) and H<sub>2</sub>O (3 mL) was heated at 90°C for 3 h. Volatiles were removed in vacuo, and the residue was lyophilized from dioxane to give Part D compound as a pink solid (75 mg), which was used in the next step without further purification.

E.

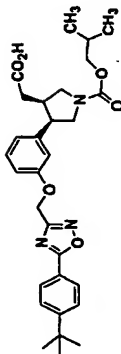


A solution of Part C compound (15 mg; 0.04 mmol) and 4-tert-butyl-benzoyl chloride (8  $\mu$ L; 0.04 mmol) in pyridine (1 mL) was heated at 115°C for 4 h, then was cooled to RT. Volatiles were removed in vacuo, and the residue was purified by preparative HPLC (YMC reverse-

- 243 -

phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 50% A to 100% B over 10 min + 5 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to furnish Part E compound.

F.



10 A solution of Part E compound and LiOH.H<sub>2</sub>O (15 mg) in 1:1 THF:H<sub>2</sub>O (2 mL) was stirred at RT for 4 h, then was acidified with aqueous 1 M HCl. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 50% A to 100% B over 10 min + 5 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) and lyophilized from dioxane to furnish the title compound as a white lyophilate (2.0 mg; 10% yield for 2 steps).

[M + H]<sup>+</sup> = 536.6

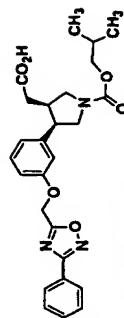
# Examples 120-122

25 Following the general procedure for the synthesis of Example 119, the following compounds of the invention were prepared.

30

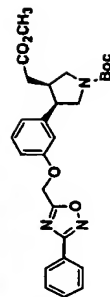
Example No.	R	[M+H] <sup>+</sup>
120		524.6
121		564.5
122		556.6

## Example 123

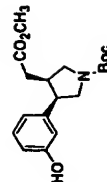


5

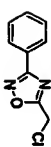
A.



10 A mixture of Example 106 Part K compound (50 mg; 0.15 mmol)

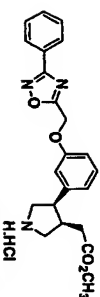


and 5-chloromethyl-3-phenyl-1-[1,2,4]oxadiazole (58 mg; 0.3 mmol),



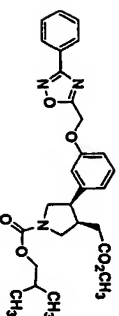
and  $K_2CO_3$  (41 mg; 0.3 mmol) in  $CH_3CN$  (10 mL) was heated at 90°C for 2 h, then cooled to RT. Solids were filtered off, and the filtrate was concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; 9:1 to 4:1 hex:EtOAc) to give Part A compound (60 mg; 82%) as a white solid.

B.



A solution of Part A compound (60 mg; 0.12 mmol) and HCl in dioxane (0.5 mL of a 4M solution; 2.0 mmol) in  $CH_2Cl_2$  (5 mL) was stirred at RT for 2 h. The reaction was concentrated to give Part B compound as a white solid (45 mg; 86%), which was used in the next step without further purification.

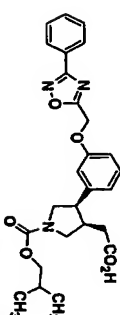
C.



A solution of Part B compound (15 mg; 0.04 mmol), isobutyl chloroformate (7  $\mu$ L, 0.06 mmol), and  $NaHCO_3$  (12 mg; 0.16 mmol) in 1:1 THF: $H_2O$  (2 mL) was stirred at RT for 30 min. Volatiles were removed in vacuo, and the residue was partitioned between EtOAc and  $H_2O$ . The organic phase was dried ( $MgSO_4$ ) and concentrated in vacuo

to give Part C compound, which was used in the next step without further purification.

D.

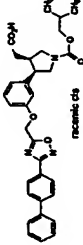
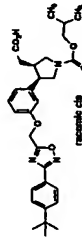


A solution of crude Part C compound and  $LiOH \cdot H_2O$  (8 mg; 0.2 mmol) in 1:1 THF: $H_2O$  (2 mL) was stirred at RT for 6 h, then was acidified to pH 2 with aqueous 1 M HCl, and finally was partitioned between EtOAc and  $H_2O$ . The organic phase was dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 50% A to 100% B over 10 min + 5 min hold time at 100% B, where A = 90:10:0.1  $H_2O$ :MeOH:TFA and B = 90:10:0.1 MeOH: $H_2O$ :TFA) and lyophilized from dioxane to furnish the title compound (11 mg; 66%) as a white solid.  $[M + H]^+ = 480.0$

#### Examples 124-125

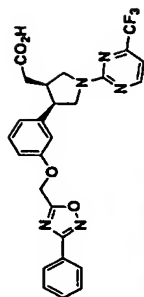
Following the general procedure for the synthesis of Example 123, the following compounds of the invention were prepared.



Example No.	R	[M+H] <sup>+</sup>
124		556.6
125		536.6

2-chloro-4-(trifluoromethyl) pyrimidine (22  $\mu$ L, 0.14 mmol), and Et<sub>3</sub>N (39  $\mu$ L; 0.28 mmol) in toluene (8 mL) was heated at 85°C for 1 h. Volatiles were removed in vacuo, and the residue was chromatographed (SiO<sub>2</sub>; 9:1 to 4:1 hex:EtOAc) to give Part A compound (36 mg; 96%) as a white solid.

B.



10

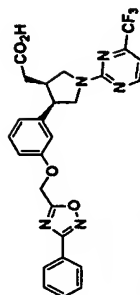
A solution of Part A compound (36 mg; 0.07 mmol) and LiOH.H<sub>2</sub>O (14 mg; 0.4 mmol) in 1:1 THF:H<sub>2</sub>O (2 mL) was stirred at RT for 18 h, then was acidified to pH 2 with aqueous 1M HCl, and finally was partitioned between EtOAc and H<sub>2</sub>O. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 50% A to 100% B over 10 min + 5 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) and lyophilized from dioxane to give the title compound as a white solid (33 mg; 94%).

[M + H]<sup>+</sup> = 526.0

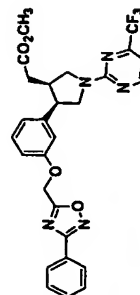
# Examples 127-130

Following the general procedure for the synthesis of Example 126, the following compounds of the invention were prepared (Example 129 was prepared using Example 89 Part B compound and Example 130 was prepared using Example 23 Part A compound).

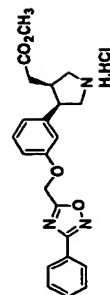
## Example 126

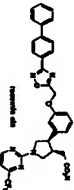
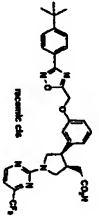
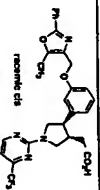
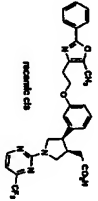


A.

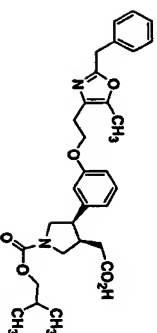


A solution of Example 123 Part B compound (30 mg; 0.07 mmol)

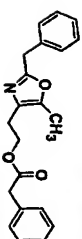


Example No.	R	[M+H] <sup>+</sup>
127		602.6
128		582.6
129		539.5
130		553.6

Example 131

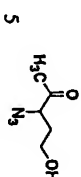


A.



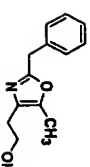
- 250 -

A mixture of 3-Azido-5-hydroxy-pentan-2-one [Example 229 Part A compound; 500 mg; 3.5 mmol]



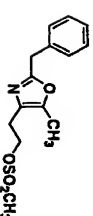
and polymer-bound PhP (1.75 g; 5.25 mmol) in dry dioxane (10 mL) was stirred at RT for 10 min, after which benzyl-carbonyl chloride (0.9 mL; 7.0 mmol) was added dropwise. The reaction was heated at 80°C for 18 h, cooled to RT and the resin was filtered off. The filtrate was concentrated in vacuo, and the residue was purified by preparative HPLC (YMC reverse-phase ODS 30 x 250 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 50% A to 100% B over 30 min + 7 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give Part A compound as an oil (200 mg; 17%).

B.



A solution of Part A compound (200 mg; 0.6 mmol), and LiOH·H<sub>2</sub>O (100 mg; 2.4 mmol) in 1:1 THF:H<sub>2</sub>O (6 mL) was heated at 50°C for 2 h, then was cooled to RT and partitioned between EtOAc and H<sub>2</sub>O. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give crude Part B compound (110 mg; 85%) as an oil, which was used in the next reaction without further purification.

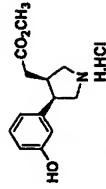
C.



- 251 -

To a 0°C solution of Part B compound (75 mg; 0.4 mmol) and Et<sub>3</sub>N (100 µL; 0.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added dropwise methanesulfonyl chloride (32 µL; 0.5 mmol). The reaction was warmed to RT and stirred at RT for 1.5 h, then was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and aqueous 1M HCl. The organic phase was washed with saturated aqueous NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 9:1 to 7:3 hex:EtOAc) to give Part C compound (95 mg; 93%) as an oil.

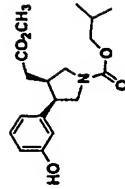
D.



15

A solution of Example 106 Part K compound (270 mg; 0.8 mmol) and HCl in dioxane (1.0 mL of a 4M solution; 4.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was stirred at RT for 2 h. Volatiles were removed in vacuo to give crude Part D compound, which was used in the next step without further purification.

E.

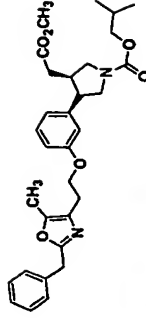


25

A solution of crude Part D compound, isobutyl chloroformate (90 µL, 0.68 mmol) and NaHCO<sub>3</sub> (336 mg; 4.0 mmol) in THF/H<sub>2</sub>O (6 mL of a 1:1 solution) was stirred at RT for 30 min, then was partitioned between EtOAc and H<sub>2</sub>O. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 3:1

hex:EtOAc) to give Part E compound (200 mg; 74% for two steps) as an oil.

F.

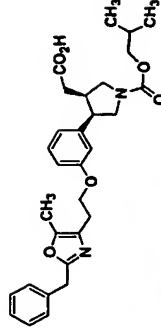


5

A mixture of Part C compound (30 mg; 0.1 mmol), Part D compound (15 mg; 0.05 mmol), and K<sub>2</sub>CO<sub>3</sub> (10 mg; 0.075 mmol) in CH<sub>3</sub>CN (1 mL) was heated at 95°C for 30 h. Volatiles were removed in vacuo, and the residue was partitioned between EtOAc and H<sub>2</sub>O. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 50% A to 100% B over 10 min + 5 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give Part F compound (13 mg; 48% yield).

20

G.



A solution of Part D compound (13 mg; 0.02 mmol) and LiOH·H<sub>2</sub>O (10 mg; 0.1 mmol) in 1:1 THF:H<sub>2</sub>O (1 mL) was stirred at RT for 18 h, then was acidified to pH 1 with 1 M aqueous HCl and finally partitioned between EtOAc and H<sub>2</sub>O. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was lyophilized from dioxane to give the title compound (9 mg; 39%) as a white solid. [M + H]<sup>+</sup> = 521.6

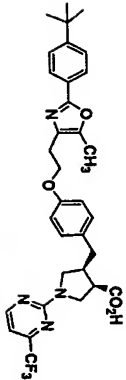
Examples 132-143

Following the general procedure for the synthesis of Example 131, the following compounds of the invention were prepared. All the appropriate arylloxazole-ethanol reagents were prepared according to the general procedure for the synthesis of Example 231 Part A compound.

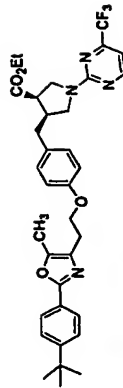
Example No.	R	[M+H] <sup>+</sup>
132		563.7
133		537.6
134		537.6
135		542.1
136		575.6
137		575.6

Example No.	R	[M+H] <sup>+</sup>
138		551.6
139		542.1
140		542.1
141		537.6
142		542.1
143		537.6

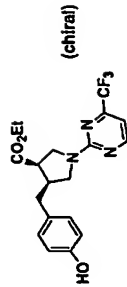
Example 144



A.



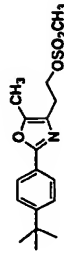
A mixture of chiral 4-(3-hydroxy-phenyl)-1-(4-trifluoromethyl-pyrimidin-2-yl)-pyrrolidine-3-carboxylic acid ethyl ester (24 mg; 0.06 mmol; obtained from chiral prep HPLC separation of Example 243 Part A compound),



10

methanesulfonic acid 2-[2-(4-tert-butylphenyl)-5-methyl-oxazol-4-yl]-ethyl ester (41 mg; 0.12 mmol; The oxazole-ethanol was prepared according to the general procedure described for the synthesis of Example 231 Part A

compound. The mesylate was prepared from the alcohol according to the general procedure described for the synthesis of Example 23 Part A compound.),



20

and  $K_2CO_3$  (14 mg; 0.09 mmol) in  $CH_3CN$  (1 mL) was heated at  $90^\circ C$  for 18 h. More  $K_2CO_3$  (14 mg; 0.09 mmol) was added and the heating was continued at  $90^\circ C$  for an additional 18 h. The reaction was then cooled to RT and volatiles were removed in vacuo. The residue was taken up in MeOH (2 mL), sonicated and filtered. The filtrate was

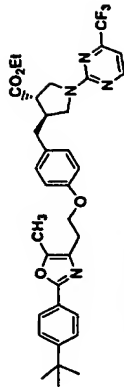
concentrated in vacuo and the residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min;

continuous gradient from 30% A to 100% B over 10 min + 6 min hold time at 100% B, where A = 90:10:0.1  $H_2O$ :MeOH:TFA

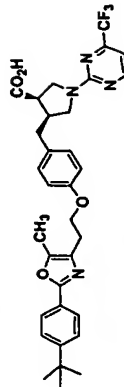
- 256 -

and B = 90:10:0.1 MeOH: $H_2O$ :TFA) to give Part A compound (cis diastereomer; 7.6 mg; 22%).

A second product isolated was Part B compound (trans diastereomer; 20 mg; 57%).



10 B.



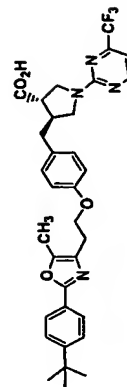
A solution of Part A compound (7.6 mg; 0.01 mmol)

and conc. HCl/HOAc (1 mL of a 1:9 solution) was heated at  $80^\circ C$  for 6 h, then was cooled to RT. Volatiles were removed in vacuo and the residue was purified by

preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min;

continuous gradient from 30% A to 100% B over 10 min + 5 min hold time at 100% B, where A = 90:10:0.1  $H_2O$ :MeOH:TFA and B = 90:10:0.1 MeOH: $H_2O$ :TFA) and was lyophilized from dioxane to give the title compound as a white solid (2.5 mg; 34% yield).  $[M + H]^+ = 609.6$

25 Example 145

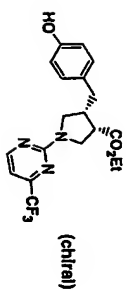


- 257 -

Following the same procedure as for Example 144 Part C, Example 144 Part B compound was converted to the title compound.  $[M + H]^+ = 609.6$

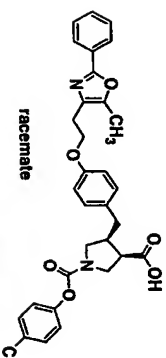
### Examples 146-147

Following the general procedure for the synthesis of Examples 144 and 145, the following compounds of the invention were prepared from the enantiomer

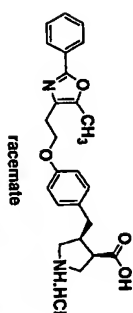


Example No.	R	$[M+H]^+$
146	<p style="text-align: center;">42 de enantiomer</p>	609.6
147	<p style="text-align: center;">42 trans enantiomer</p>	609.6

### Example 148

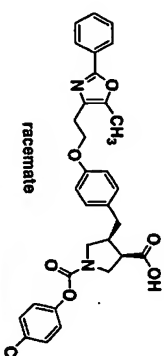


A.



A solution of Example 23 Part F compound (240 mg; 0.45 mmol) in HOAc (20 mL) and aqueous HCl (20% solution; 5 mL) was stirred at 85°C for 4 h, then was cooled to RT and concentrated in vacuo to give Part A compound (200 mg; 100%) as an oil.

B.



A mixture of part A compound (20 mg; 0.037 mmol),  $\text{NaHCO}_3$  (8 mg; 0.09 mmol) and 4-chlorophenyl chloroformate (10  $\mu\text{L}$ ; 0.074 mmol) in THF (0.5 mL) and water (50  $\mu\text{L}$ ) was stirred at RT for 1 h, then concentrated in vacuo. The residue was partitioned between EtOAc (2 mL) and saturated  $\text{KHSO}_4$  (1 mL). The organic phase was washed with brine (1 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 1) and lyophilized (water) to give the title compound (18.3 mg; 66%) as an oil.

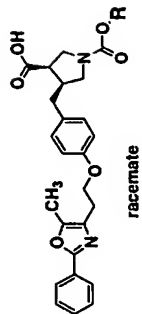
$[M + H]^+ = 561.2$

### Examples 149-157

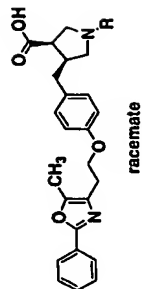
Compounds 149-157 of the invention were prepared (from Example 148 part A compound) in a similar fashion to the synthesis of Example 148 using appropriate chloroformates.

Examples 158-163

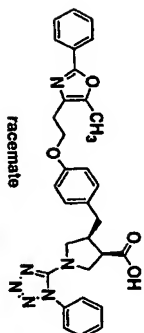
Examples 158-163 of the invention were prepared (from Example 148 part A compound) in a similar fashion to the synthesis of Example 148 using appropriate acylating reagents.



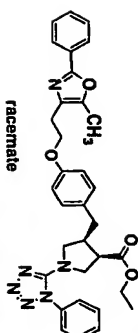
Example #	R	[M + H] <sup>+</sup>
149		541.3
150		507.3
151		493.3
152		507.3
153		541.3
154		557.2
155		509.3
156		521.3
157		527.2



Example #	R	Reagent	[M + H] <sup>+</sup>
158			517.2
159			547.2
160			506.3
161			491.1
162			505.1
163			506.1

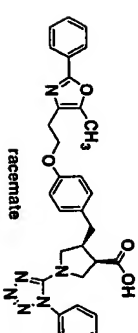
Example 164

5 A.



A solution of Example 31 Part A compound (5 mg; 0.012 mmol), 5-chloro-1-phenyl-tetrazole (15  $\mu$ L; 0.11 mmol), Et<sub>3</sub>N (40  $\mu$ L; 0.29 mmol) in toluene (1 mL) was stirred at 120°C in a sealed tube for 18h; then was cooled to RT and concentrated in vacuo. The residue was partitioned between EtOAc (10 mL) and brine (5 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 1) and lyophilized (water) to give Part A compound (5 mg; 75%) as an oil.

B.



A solution of Part A compound (5 mg; 0.0087 mmol) in HOAc (0.8 mL) and aqueous HCl (0.2 mL of a 20% solution) was stirred at 88°C for 4 h; then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1) and

lyophilized (water) to give the title compound (2 mg; 42%) as an oil.

[M + H]<sup>+</sup> = 551.2

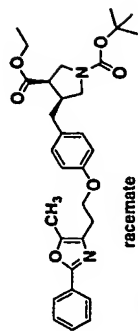
<sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  7.86 (m, 2 H), 7.38 (m, 8 H), 6.87 (m, 2 H), 6.69 (m, 2 H), 4.12 (t, J = 7 Hz, 2 H), 3.49 (m, 1H), 3.40 (m, 1 H), 3.06 (m, 1 H), 3.01 (m, 2 H), 2.88 (t, J = 7 Hz, 2 H), 2.67 (m, 1 H), 2.58 (m, 1 H), 2.36 (m, 1 H), 2.28 (s, 3H)

10 Examples 165-169

Examples 165 through 169 of the invention were prepared in a similar fashion to the synthesis of Example 164 (from Example 31 Part A compound) using appropriate heteroaryl chlorides.

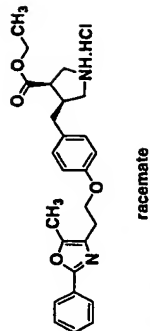


A.



A mixture of Example 23 Part E compound (1.00 g; 2.9 mmol), 5-phenyl-2-methyl-oxazole-4-ethanol (700 mg; 3.4 mmol) and cyanomethylene tributylphosphorane (830 mg; 3.5 mmol) in toluene (15 mL) was stirred at 85°C for 4h, then was cooled to RT and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 7:3 to 3:7 hex:EtOA) to give Part A compound (1.30 g; 85%) as an oil.

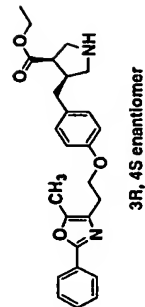
B.



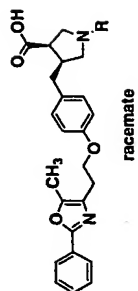
15

A solution of Part A compound (1.3 g; 2.4 mmol) in DCE (10 mL) and HCl in dioxane (2.5 mL of a 4M solution; 10 mmol) was stirred at RT for 3 h; then was concentrated in vacuo. The residue was partitioned between EtOAc (30 mL) and saturated aqueous NaHCO<sub>3</sub> (10 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give Part B compound (530 mg; 50%; racemate) as a colorless oil.

C.



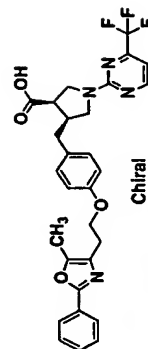
25



Example #	R	[M + H] <sup>+</sup>
165		535.2
166		568.1
167		586.1
168		499.2
169		514.2

5

# Example 170



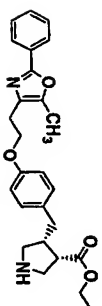
10

The individual enantiomers of racemic Part B compound (530 mg; 1.2 mmol) were separated by preparative HPLC using the following conditions: Chiralpak AD chiral column, 5 cm X 50 cm, 20 $\mu$ ; Isocratic solvent system: 15:85 A:B (A = 50% MeOH + 50% EtOH + 0.1% Et<sub>3</sub>NH; B = 100% heptane + 0.1% Et<sub>3</sub>NH); Injection volume = 10 mL MeOH; Detection wavelength = 220 nm; Flow rate = 50 mL/min. The enantiomer that eluted off the column first was Part C compound (245 mg; 46 mg), which was isolated as an oil.

Analytical chiral HPLC conditions: Chiralpak AD chiral column 4.6 X 250 mm; Isocratic solvent system: 15%A + 85%B, where Solvent A = 50% MeOH + 50% EtOH + 0.1% Et<sub>3</sub>NH; Solvent B = 100% heptane + 0.1% Et<sub>3</sub>NH; Detection wavelength = 254 nm; Flow rate = 1 mL/min; Retention time = 13.3 min. [ $\alpha$ ] (0.48w/v%)<sub>MeOH</sub><sup>589</sup> = +10.9°.

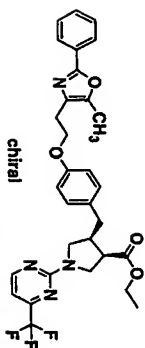
The other enantiomer from Part B compound (that eluted off the column later than Part C compound) was identified as Part D compound (245 mg; 46%), which was isolated as an oil. Under the identical chiral analytical HPLC conditions as for Part C compound, the retention time of Part D compound = 26.7 min. [ $\alpha$ ] (0.50w/v%)<sub>MeOH</sub><sup>589</sup> = -12.3°.

D.



3S, 4R enantiomer

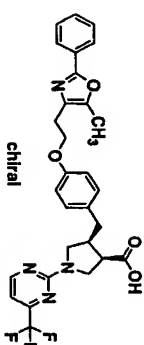
E.



chiral

A solution of Part C compound (225 mg; 0.52 mmol), 2-chloro-4-trifluoromethylpyrimidine (77  $\mu$ l; 0.64 mmol), Et<sub>3</sub>N (130  $\mu$ l; 0.93 mmol) in toluene (4.5 mL) was stirred at 60°C in a sealed tube for 3 h; then was cooled to RT and concentrated in vacuo. The residue was partitioned between EtOAc (10 mL) and brine (5 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 1:1 hex:EtOAc) to provide Part E compound (300 mg; 100%) as a colorless oil.

F.



chiral

A solution of Part E compound (300 mg; 0.52 mmol) in HOAc (4 mL) and aqueous HCl (1 mL of a 20% solution) was stirred at 70°C for 18h; then was cooled to RT and concentrated in vacuo. The residue was partitioned between EtOAc (30 mL) and water (10 mL). The organic layer was washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 1) and lyophilized (dioxane) to give the title compound (230 mg; 81%) as a white solid.

[M + H]<sup>+</sup> = 553.2[ $\alpha$ ] (0.96w/v%)<sub>MeOH</sub><sup>589</sup> = -70.8°

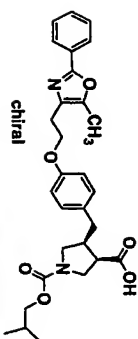
Analytical chiral HPLC: Chiralpak AD chiral column 4.6 X 250 mm, 10 $\mu$ ; Isocratic solvent system: 3:7 A:B, where Solvent A = 100% IPA + 0.1% TFA; Solvent B = 100% heptane Detection = 254 nm; Flow rate = 2 mL/min; Retention time = 6.7 min.

<sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  8.41 (m, 1H), 7.85 (m, 2H), 7.36 (m, 3H), 7.00 (d, J = 9 Hz, 2H), 6.76 (m, 3H), 4.13 (m, 2



1 H), 2.87 (m, 2H), 2.73 (m, 2 H), 2.41 (m, 1 H), 2.28 (s, 3H)

### Example 172

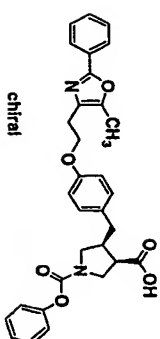


The title compound was prepared from the reaction of Example 170 Part C compound (131 mg; 0.30 mmol) with isobutyl chloroformate (50  $\mu$ L; 0.45 mmol) using the same 2-step sequence as employed in the synthesis of Example 148 from Example 170 Part C compound. The title compound was obtained (75 mg; 44%) as a white solid after preparative HPLC (using the same conditions as described in Example 1)

[M + H]<sup>+</sup> = 507.2

<sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  7.86 (m, 2H), 7.37 (m, 3 H), 6.99 (m, 2 H), 7.75 (m, 2 H), 4.13 (m, 2 H), 3.72 (m, 2H), 3.58 (m, 1 H), 3.41 (m, 1 H), 3.21 (m, 3 H), 3.03 (m, 1H), 2.87 (m, 2 H), 2.71 (m, 1 H), 2.59 (m, 1 H), 2.33 (m, 1H), 1.80 (s, 3H), 0.81 (q, J = 7 Hz, 6H)

### Example 173



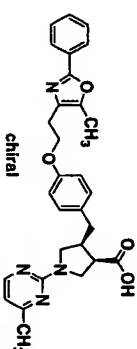
The title compound was prepared from the reaction of Example 170 Part C compound (109 mg; 0.25 mmol) with phenyl chloroformate (50  $\mu$ L; 0.45 mmol) using the same 2-

step sequence as employed in the synthesis of Example 148 from Example 170 Part C compound. The title compound was obtained (80 mg; 61%) as a white solid after preparative HPLC (using the same conditions as described for the purification of Example 1 compound)

[M + H]<sup>+</sup> = 527.2

<sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  7.85 (m, 2H), 7.37 (m, 3 H), 7.26 (m, 2 H), 7.10 (m, 1 H), 7.00 (m, 4 H), 6.78 (m, 2 H), 4.13 (m, 2 H), 3.80 (m, 1H), 3.65 (m, 1 H), 3.45 (m, 1 H), 3.24 (m, 1H), 3.11 (m, 1 H), 2.87 (m, 2 H), 2.74 (m, 1 H), 2.66 (m, 1H), 2.42 (m, 1H), 2.27 (d, J = 5 Hz, 3H)

### Example 174



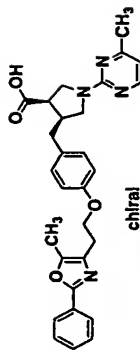
A.



To a -40°C suspension of 2-chloropyrimidine (2.8 mL; 24.6 mmol) in Et<sub>2</sub>O (75 mL) was added a solution of methyl lithium in Et<sub>2</sub>O (20 mL of a 1.4 M solution; 28 mmol). The mixture was stirred at -40°C for 30 min, then was allowed to warm to 0°C and stirred at 0°C for 30 min. After cooling to -40°C, a solution of HOAc (1.7 mL), water (0.3 mL) and THF (10 mL) was added dropwise, followed by a solution of DDQ (7.0 g in 25 mL THF). The mixture was allowed to warm to RT and was stirred at RT for 10 min, then cooled to 0°C. Aqueous NaOH (1.2 g in 10 mL of H<sub>2</sub>O) was added, and the mixture was stirred at 0°C for 10 min. The organic phase was dried (MgSO<sub>4</sub>/K<sub>2</sub>CO<sub>3</sub>)

and concentrated in vacuo to give Part A compound (1.1 g; 35%) as a solid.

B.



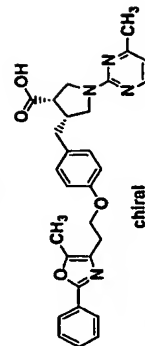
5

The title compound was prepared from the reaction of Example 170 Part C compound (100 mg; 0.24 mmol) with Part A compound (34 mg; 0.26 mmol) using the same 2-step sequence as employed in the synthesis of Example 170 from Example 170 Part C compound. The title compound was obtained (90 mg; 78%) as a white solid after preparative HPLC (using the same conditions as described in Example 1).

15  $[M + H]^+ = 499.2$ 

Analytical chiral HPLC: Chiral AD column; 4.6 X 250 mm, 10 $\mu$ ; Isocratic solvent system: 20%A + 80%B; Solvent A = 100% IPA + 0.1% TFA; Solvent B = 100% heptane + 0.1% TFA; Detection = 261 nm; Flow rate = 1 mL/min; Retention time = 10.86 min.

$^1H$  NMR ( $CD_3OD$ ):  $\delta$  8.13 (m, 1H), 7.94 (m, 2 H), 7.46 (m, 3 H), 7.14 (m, 2 H), 6.86 (m, 3 H), 4.22 (t, J = 6 Hz, 2 H), 4.12 (m, 1H), 3.83 (m, 1H), 3.57 (m, 1H), 3.42 (m, 1H), 3.32 (m, 1H), 2.97 (m, 4H), 2.55 (m, 4H), 2.39 (s, 3H)

Example 175

30

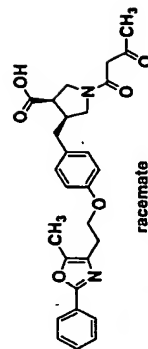
The title compound was prepared from Example 170 Part D compound (60 mg; 0.14 mmol) with Example 174 Part A compound (23 mg; 0.18 mmol) using the 2-step sequence as employed in the synthesis of Example 170 from Example 170 Part D compound. The title compound was obtained (50 mg; 73%) as a white solid after preparative HPLC (using the same conditions as described in Example 1)

 $[M + H]^+ = 499.2$ 

10 Chiral Analytical HPLC: Chiralpak AD chiral column; 4.6 X 250 mm, 10 $\mu$ ; Isocratic solvent system: 20%A + 80%B; Solvent A = 100% IPA + 0.1% TFA; Solvent B = 100% heptane + 0.1% TFA; Detection = 261 nm; Flow rate = 1 mL/min

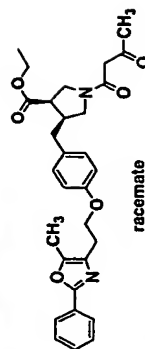
15 Retention time = 17.32 min.

$^1H$  NMR ( $CD_3OD$ ):  $\delta$  8.17 (m, 1H), 7.94 (m, 2 H), 7.45 (m, 3 H), 7.13 (m, 2 H), 6.85 (m, 3 H), 4.20 (t, J = 6 Hz, 2 H), 4.11 (m, 1H), 3.83 (m, 1H), 3.57 (m, 1H), 3.42 (m, 1H), 3.32 (m, 1H), 2.97 (m, 4H), 2.55 (m, 4H), 2.39 (s, 3H)

Example 176

25

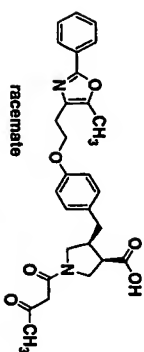
A.



30

A solution of Example 31 Part A compound (600 mg; 1.38 mmol) and diketene (126  $\mu$ L; 1.7 mmol) in MeCN (4 mL) was stirred at 70°C for 4 h, then was cooled to RT and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% EtOAc to 1:4 MeOH/EtOAc) to give Part A compound (450 mg; 63%) as an oil.

## B.

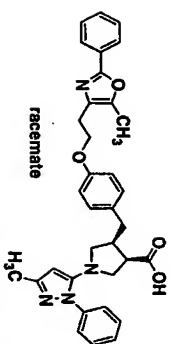


A solution of Part A compound (15 mg; 0.029 mmol) in HOAc (0.8 mL) and aqueous HCl (0.2 mL of a 20% solution) was stirred at 70°C for 18 h; then was cooled to RT and concentrated in vacuo. The residue was purified by lyophilized (water) to give the title compound (8 mg; 56%) as an oil.

[M + H]<sup>+</sup> = 491.2

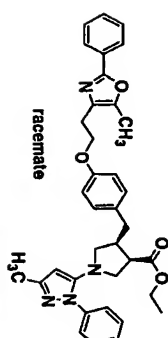
<sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  7.86 (m, 2H), 7.37 (m, 3H), 7.00 (m, 2H), 6.76 (m, 2H), 4.13 (t, J = 6 Hz, 2H), 3.67 (m, 1H), 3.59 (m, 1H), 3.26 (m, 2H), 3.20 (m, 2H), 3.15 (m, 1H), 3.05 (m, 1H), 2.87 (m, 2H), 2.70 (m, 1H), 2.37 (m, 1H), 2.28 (s, 3H), 2.10 (m, 3H)

## Example 177



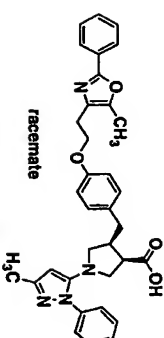
30

## A.



To a solution of Example 176 Part A compound (100 mg; 0.19 mmol) and phenylhydrazine (19  $\mu$ L; 0.19 mmol) in EtOH (1 mL), was added methanesulfonic acid (6  $\mu$ L). The mixture was stirred at RT for 3 h; then pyridine (100  $\mu$ L) was added and the mixture was concentrated in vacuo. The residue was dissolved in pyridine (1 mL) and POCl<sub>3</sub> (54  $\mu$ L; 0.58 mmol) was added. The mixture was stirred at RT for 18 h, after which the reaction was quenched by adding water (0.2 mL). The mixture was partitioned between EtOAc (10 mL) and saturated aqueous NaHCO<sub>3</sub> (5 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 1) and lyophilized (water) to give the title compound (18 mg; 17%) as an oil.

## B.



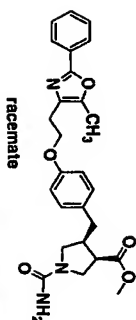
Example 177 title compound (3.4 mg; 71%) was prepared from Part A compound (5 mg; 0.008 mmol) using the same procedure as described in Example 164 title compound.

[M + H]<sup>+</sup> = 563.3

<sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  7.95 (m, 2H), 7.53 (m, 5H), 7.46 (m, 4H), 7.94 (m, 2H), 6.78 (m, 2H), 4.20 (t, J = 6 Hz, 2H), 3.42 (m, 1H), 3.36 (m, 1H), 3.24 (m, 1H), 2.97 (m,

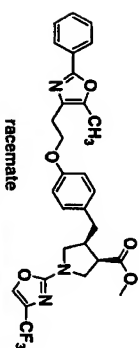


B.



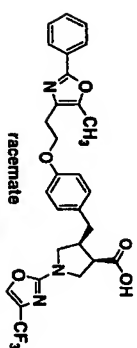
A solution of Part A compound (50 mg; 0.12 mmol) and trimethylsilylisocyanate (20  $\mu$ L; 0.14 mmol) in THF (1 mL) was stirred at RT for 18 h. Volatiles were removed in vacuo and the residue was partitioned between EtOAc (10 mL) and brine (5 mL). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give Part B compound (60 mg; 100%) as an oil.

C.



A solution of Part B compound (60 mg; 0.13 mmol) and bromotrifluoroacetone (17  $\mu$ L; mmol) in toluene (1.5 mL) was stirred at 80°C for 3 h. Volatiles were removed in vacuo and the residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 85:15 to 2:3 hex:EtOAc) to provide compound (25 mg; 35%) as a colorless oil.

D.



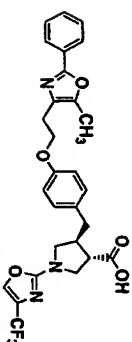
A solution of Part C compound (8 mg; 0.014 mmol) and  $\text{LiOH} \cdot \text{H}_2\text{O}$  (4 mg; 0.092 mmol) in THF (0.33 mL), MeOH (0.15 mL) and  $\text{H}_2\text{O}$  (0.15 mL) was stirred at RT for 1 h, then was concentrated in vacuo. The residue was

partitioned between aqueous HCl (5 mL) and EtOAc (20 mL). The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 1) and lyophilized (dioxane) to give the title compound (2.1 mg; 27%) as a solid.

$[\text{M} + \text{H}]^+ = 542.3$

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.95 (m, 2H), 7.84 (m, 1H), 7.46 (m, 3H), 7.12 (d,  $J = 8$  Hz, 2H), 6.86 (d,  $J = 8$  Hz, 2H), 4.22 (t,  $J = 4$  Hz, 2H), 3.83 (m, 1H), 3.69 (m, 1H), 3.45 (m, 1H), 3.38 (m, 1H), 3.24 (m, 1H), 2.96 (t,  $J = 8$  Hz, 2H), 2.84 (m, 2H), 2.49 (m, 1H), 2.37 (m, 3H)

In addition, a second, slower eluting fraction from the preparative HPLC of the crude hydrolysis product mixture was identified as the epimerized trans-isomer Example 181 (2.0 mg; 26%):



20

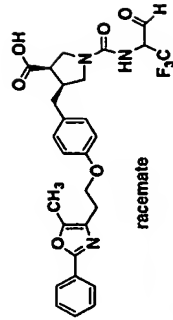
#### Example 181

$[\text{M} + \text{H}]^+ = 542.3$

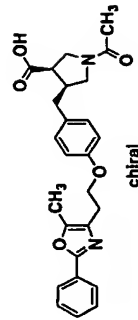
$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.95 (m, 2H), 7.84 (m, 1H), 7.46 (m, 3H), 7.12 (d,  $J = 8$  Hz, 2H), 6.86 (d,  $J = 8$  Hz, 2H), 4.22 (t,  $J = 4$  Hz, 2H), 3.81 (m, 1H), 3.72 (m, 1H), 3.54 (m, 1H), 3.30 (m, 1H), 2.97 (m, 3H), 2.90 (m, 1H), 2.80 (m, 1H), 2.63 (m, 1H), 2.37 (m, 3H)

30



Example 182

- 5 solution of Example 180 Part C compound (15 mg; 0.03 mmol) in HOAc (0.8 mL) and aqueous HCl (0.2 mL of a 20% solution) was stirred at 70°C for 3 days. The mixture was concentrated in vacuo and the residue was purified by preparative HPLC (as described for Example 1) and lyophilized (water) to give the title compound (13 mg; 86%) as an oil.
- 10  $[M + H]^+ = 559.2$

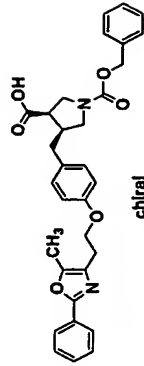
Example 183

15

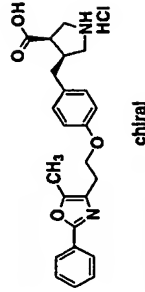
- The title compound (5 mg; 9.6%) was prepared employing the same procedure as described in Example 164
- 20 Part B compound from Example 170 Part C compound (50 mg; 0.12 mmol).

 $[M + H]^+ = 449.4$ 

- 25  $^1H$  NMR ( $CD_3OD$ ):  $\delta$  8.01 (m, 2H), 7.53 (m, 3H), 7.15 (t, J = 9 Hz, 2H), 6.91 (m, 2H), 4.27 (t, J = 4 Hz, 2H), 3.84 (m, 1H), 3.74 (m, 1H), 3.65 (m, 1H), 3.49 (m, 1H), 3.29 (m, 1H), 3.17 (m, 1H), 3.03 (m, 2H), 2.73 (m, 1H), 2.51 (m, 1H), 2.45 (m, 3H), 2.03 (m, 3H)

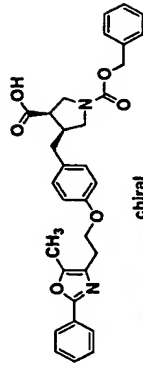
Example 184

5 A.



- Part A compound (186 mg; 100%) was prepared from Example 170 Part C compound (200 mg; 0.46 mmol) using the procedure described in Example 148 Part A compound.
- 10

B.



- 15 The title compound was prepared from the reaction of Part A compound (15 mg; 0.035 mmol) with benzyl chloroformate (15  $\mu$ L; 0.14 mmol) using the procedure as employed in the synthesis of Example 148. The title compound was obtained (10 mg; 54%) as an oil after preparative HPLC (using the same conditions as described in Example 1)
- 20

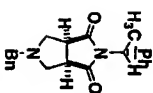
 $[M + H]^+ = 541.3$ 

- 25  $^1H$  NMR ( $CD_3OD$ ):  $\delta$  7.95 (m, 2H), 7.48 (m, 3H), 7.33 (m, 5H), 7.05 (m, 2H), 6.83 (m, 2H), 5.10 (m, 2H), 4.22 (t, J = 4 Hz, 2H), 3.71 (m, 1H), 3.52 (m, 1H), 3.30 (m, 2H), 3.12 (m, 1H), 2.96 (m, 2H), 2.78 (m, 1H), 2.69 (m, 1H), 2.42 (m, 1H), 2.37 (m, 3H)

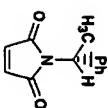
$[\alpha]_D^{25} (0.97\text{w/v\%})_{\text{MeCN}} = -33.7^\circ$

An alternative synthesis of Example 184 compound is shown using the following sequence:

C.

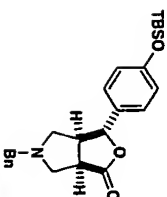


To a  $0^\circ\text{C}$  solution of (R)-(+)-(1-phenylethyl) maleimide (3 g; 15 mmol)



and Example 1 Part B compound (4.56 g; 19.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) was added TFA (0.1 mL). The solution was allowed to warm to RT and stirred at RT for 2 h, then was concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; 4:1 hex:EtOAc) to give Part C compound (4.2 g; 84%) as a white solid.

D.

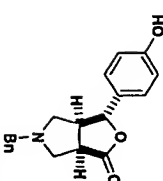


To a  $-20^\circ\text{C}$  ( $\text{CCl}_4$ /dry ice bath) solution of Part C Compound (1.5 g; 4.4 mmol) in THF (5 mL) was 4-tert-butylidimethylsilyloxyphenyl magnesium bromide in THF (15 mL of a 0.58 M solution) over 1 h using a syringe pump.

- 282 -

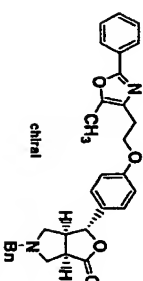
The reaction was complete by HPLC 30 min after the addition had been completed, after which EtOH (30 mL) was added followed by  $\text{NaBH}_4$  (0.42 g; 11 mmol). The mixture was stirred for 2 h at  $0^\circ\text{C}$  and for 18 h at RT. The mixture was concentrated in vacuo and the residue was partitioned between EtOAc and aqueous 10%  $\text{K}_2\text{CO}_3$ . The organic layer was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was dissolved in toluene (50 mL) and the mixture was stirred at  $110^\circ\text{C}$  for 8 h, then was cooled to RT and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; 9:1 hex:EtOAc) to give Part D compound as a clear oil (0.92 g; 45%).

E.



To a  $0^\circ\text{C}$  solution of Part D compound (500 mg; 1.18 mmol) in THF (5 mL) was added (n-Bu) $_4\text{NF}$  (1.3 mL of a 1 M solution in THF; 1.0 mmol). The mixture was stirred at  $0^\circ\text{C}$  for 30 min, then was concentrated in vacuo to give crude Part E compound (360 mg; 99%) as an oil.

F.

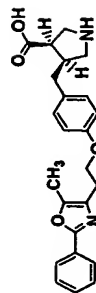


A mixture of crude Part E compound (360 mg; 1.2 mmol) in MeCN (10 mL), Example 23 Part A compound (400 mg; 1.42 mmol) and  $\text{K}_2\text{CO}_3$  (196 mg; 1.42 mmol) was stirred at  $85^\circ\text{C}$  for 18 h, then was cooled to RT and concentrated in vacuo. The residue was partitioned between EtOAc (20

- 283 -

mL) and brine (10 mL). The organic layer was separated, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was chromatographed (SiO<sub>2</sub>; gradient from 100% hex to 3:7 hex:EtOAc) to give Part F compound (320 mg; 55%) as a colorless oil.

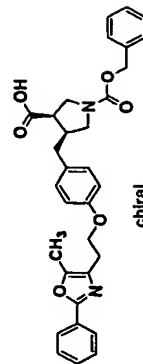
G.



3S, 4R enantiomer

10 A mixture of Part F compound (600 mg; 1.2 mmol) and 10% Pd/C (30 mg) in HOAc (24 mL) was stirred under an atmosphere of H<sub>2</sub> (60 psi) for 18 h. The mixture was filtered through Celite®; the Celite® pad was washed with MeOH (30 mL). The combined filtrates were concentrated in vacuo to give Part G compound (500 mg; 100%) as an oil. This material was confirmed to be the 3S, 4R enantiomer by conversion to Example 170 Part C compound (see Example 170).

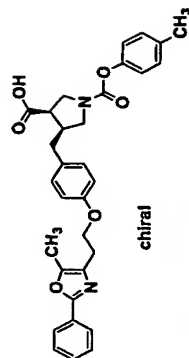
20 H.



chiral

The title compound (130 mg; 75%) was prepared from the reaction of Part G compound (130 mg; 0.32 mmol) with benzyl chloroformate (46  $\mu$ L; 0.32 mmol) using the same procedure as described for the synthesis of Example 148 Part B compound.

30

Example 185

chiral

5 The title compound was prepared from Example 184 Part A compound (15 mg; 0.035 mmol) with p-tolyl chloroformate (10  $\mu$ L; 0.09 mmol) using the procedure as

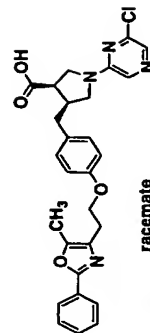
employed in the synthesis of Example 148. The title compound (10 mg; 54%) was obtained as an oil after preparative HPLC (using the same conditions as described in Example 1).

[M + H]<sup>+</sup> = 541.3

<sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  7.95 (m, 2H), 7.47 (m, 3H), 7.13 (m, 4H), 6.95 (m, 2H), 6.86 (m, 2H), 4.22 (t, J = 4 Hz, 2H), 3.86 (m, 1H), 3.74 (m, 1H), 3.52 (m, 1H), 3.33 (m, 1H), 3.20 (m, 1H), 2.98 (m, 2H), 2.84 (m, 1H), 2.75 (m, 1H), 2.49 (m, 1H), 2.36 (m, 3H), 2.31 (s, 3H), [ $\alpha$ ] (0.69% v/v%<sub>MeOH</sub>)<sub>25</sub> = -50.6°

20 Example 185 (135 mg; 78%) was also prepared from Example 184 Part B compound (130 mg; 0.32 mmol) with p-tolyl chloroformate (50  $\mu$ L; 0.35 mmol) using the same procedure as described for the synthesis of Example 148 Part B compound.

25

Example 186

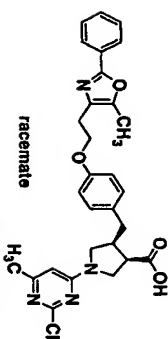
racemate

The title compound (5 mg; 20%) was prepared from

Example 180 Part A compound (20 mg; 0.048 mmol) with 2,6-dichloropyrazine (15 mg; 0.10 mmol) using the same procedure as described for the synthesis of Example 164.

[M + H]<sup>+</sup> = 519.2

#### Example 187



10

The title compound (6 mg; 18%) was prepared from Example 148 Part A compound (25 mg; 0.062 mmol) with 2,4-dichloro-6-methylpyrimidine (15 mg; 0.092 mmol) using the procedure described in Example 164 Part A compound.

[M + H]<sup>+</sup> = 533.1

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.95 (m, 2H), 7.46 (m, 3H), 7.12 (m, 2H), 6.87 (d, J = 4Hz, 2H), 6.50 (m, 1H), 4.21 (m, 2H), 4.07 (m, 1H), 3.83 (m, 1H), 3.70 (m, 1H), 3.62 (m, 1H), 3.51 (m, 1H), 3.37 (m, 1H), 2.97 (m, 2H), 2.90 (m, 1H), 2.50 (m, 1H), 2.37 (s, 3H), 2.34 (m, 3H)

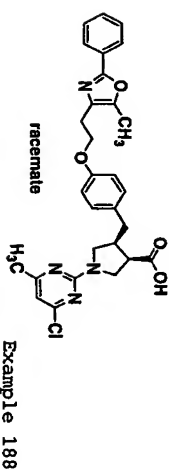
20

A second compound (later fraction), identified as Example 188 (3 mg; 9%) was also obtained from the preparative HPLC purification.

[M + H]<sup>+</sup> = 533.1

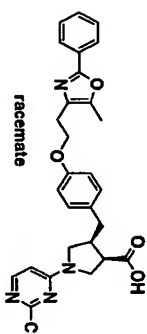
<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 7.95 (m, 2H), 7.46 (m, 3H), 7.12 (m, 2H), 6.87 (d, J = 4Hz, 2H), 6.67 (m, 1H), 4.24 (m, 2H), 3.97 (m, 1H), 3.74 (m, 1H), 3.54 (m, 1H), 3.43 (m, 1H), 3.30 (m, 2H), 2.97 (m, 2H), 2.86 (m, 1H), 2.50 (m, 1H), 2.38 (m, 6H)

30



5

#### Example 189



The title compound (5 mg; 18%) was prepared from

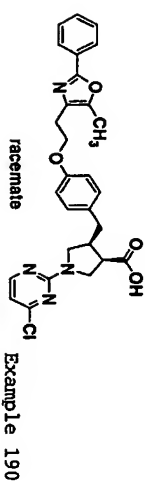
Example 148 Part A compound (20 mg; 0.050 mmol) with 2,4-dichloropyrimidine (15 mg; 0.10 mmol) using the same procedure as described for the synthesis of Example 164 Part A compound.

[M + H]<sup>+</sup> = 519.2

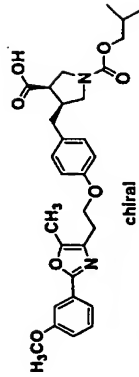
A second compound (later fraction), identified as Example 190 (2 mg; 8%) was also obtained from the preparative HPLC purification.

[M + H]<sup>+</sup> = 519.1

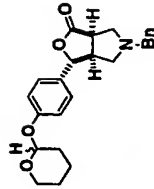
20



## Example 191

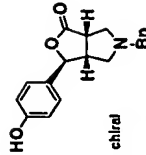


5 A.



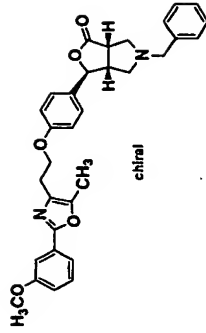
Part A compound was synthesized from (R)-(+)-(1-phenylethyl)maleimide employing the identical synthetic sequence used for the synthesis of Example 184 Part D compound except that 4-tetrahydropyranyloxy-phenyl magnesium bromide was used instead of 4-tert-butylidimethylsilyloxy-phenyl magnesium bromide.

15 B.



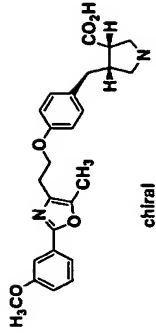
A solution of Part A compound (200 mg; 0.51 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at RT and p-toluenesulfonic acid. $\text{H}_2\text{O}$  (116 mg; 0.61 mmol) was stirred at RT for 4 h; then was concentrated in vacuo to give crude Part B compound (150 mg; 96%).

C.



Part C compound (30 mg; 58%) was prepared by the reaction of crude Part B compound (30 mg; 0.097 mmol) with the mesylate Example 277 Part E compound (33 mg; 0.11 mmol) using the procedure described in Example 184 Part F compound.

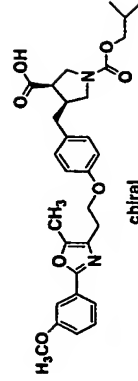
D.



10

Part D compound (20 mg; 100%) was prepared from Part C compound (30 mg; 0.057 mmol) using the procedure described for the preparation of Example 184 Part G compound.

F.



15

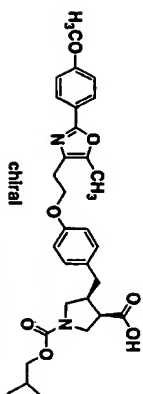
The title compound (20 mg; 65%) was prepared from Part D compound (20 mg; 0.057 mmol) and isobutyl chloroformate (8  $\mu\text{L}$ ; 0.057 mmol) using the same procedure as described for the synthesis of Example 148 compound.

$[M + H]^+ = 537.4$

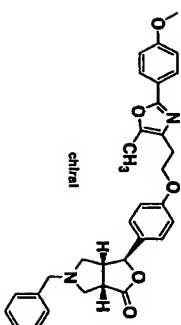
$^1\text{H NMR}$  ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.51 (m, 2H), 7.37 (m, 1H), 7.07 (d, J = 8 Hz, 2H), 7.01 (d, J = 8 Hz, 1H), 6.84 (d, J = 8 Hz,

2H), 4.21 (m, 2H), 3.84 (s, 3H), 3.81 (m, 2H), 3.67 (m, 1H), 3.50 (m, 1H), 3.29 (m, 2H), 3.12 (m, 1H), 2.95 (m, 2H), 2.79 (m, 1H), 2.68 (m, 1H), 2.42 (m, 1H), 2.36 (s, 3H), 1.89 (m, 1H), 0.89 (dd, J = 6 Hz, 6H)

### Example 192

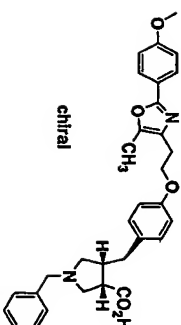


10 A.



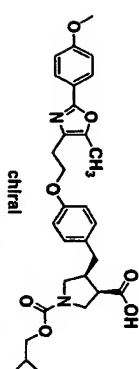
15 Part A compound (30 mg; 58%) was prepared by the reaction of Example 191 Part B compound (30 mg; 0.097 mmol) with the mesylate Example 264 Part B compound (33 mg; 0.11 mmol) using the procedure described for the preparation of Example 184 Part F compound.

B.



20 Part B compound (20 mg; 100%) was prepared from Part A compound (30 mg; 0.057 mmol) using the procedure described in Example 184 Part G compound.

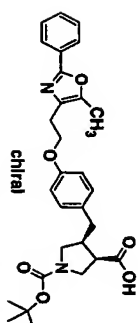
C.



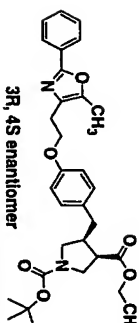
5 Part C compound (15 mg; 49%) was prepared from Part B compound (20 mg; 0.057 mmol) with isobutyl chloroformate (8  $\mu$ L; 0.057 mmol) using the procedure described for the synthesis of Example 148. [M + H]<sup>+</sup> = 537.3

10

### Example 193



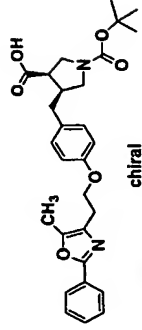
A.



25 Part A compound (the 3R, 4S enantiomer; 200 mg; 25%) was isolated from racemic Example 23 Part F compound (800 mg; 1.50 mmol) by preparative HPLC using the following conditions: Chiralpak AD column, 5 cm X 50 cm, 20 $\mu$ ; Isocratic solvent system: 10%A:90%B (A = 100% IPA + 0.1% HOAc; B = 100% hex + 0.1% HOAc); Injection volume = 10 mL in IPA; Detection = 220 nm; Flow rate = 50 mL/min. Analytical chiral HPLC: Chiralpak AD column 4.6 X 250 mm Isocratic solvent system: 10%A + 90%B; Solvent A = 100% IPA + 0.1% HOAc; Solvent B = 100% hex + 0.1% HOAc; Detection = 254 nm; Flow rate = 1 mL/min

Retention time = 5.7 min.

B.



5

A solution of Part A compound (5 mg; 0.0094 mmol) in HOAc (1 mL) and aqueous HCl (0.25 mL of a 20% solution) was stirred at 85°C for 18 h. Volatiles were removed in vacuo, and the residue was dissolved in THF (1 mL). Saturated aqueous NaHCO<sub>3</sub> (0.5 mL) and di-tert-butyl dicarbonate (10 mg; 0.046 mmol) were added. The reaction was stirred at RT for 3 h, then was quenched by the addition of saturated aqueous NH<sub>4</sub>Cl (0.5 mL). The mixture was partitioned between EtOAc (50 mL) and saturated aqueous NH<sub>4</sub>Cl (10 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1) and lyophilized (water) to give the title compound (3 mg; 63%) as a white solid.

20 [M + H]<sup>+</sup> = 506.6

Part B compound was also prepared from Example 170 Part C compound using the following synthetic route:

25 A solution of Example 170 Part C compound (350 mg; 0.81 mmol) in HOAc (4 mL) and aqueous HCl (1 mL of a 20% solution) was stirred at 85°C for 6 h. Volatiles were removed in vacuo and the residue was dissolved in THF (5 mL); the pH was adjusted to ~9 with saturated aqueous NaHCO<sub>3</sub>, after which (Boc)<sub>2</sub>O (280 mg; 1.28 mmol) was added. The reaction was stirred at RT for 18 h, then was quenched with saturated aqueous NH<sub>4</sub>Cl solution (50 mL) to adjust the pH to ~3-4. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was

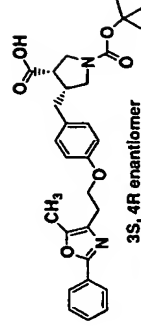
- 292 -

chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to give a yellow oil, which was lyophilized from dioxane to give the title compound (250 mg; 61%) as a light yellow solid.

5 [M + H]<sup>+</sup> = 506.6

[α] (12 mg/2 mL) MeOH<sup>589</sup> = -33.67°

#### Example 194



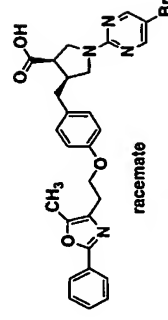
10

The title compound (150 mg; 61%) was prepared from Example 170 Part D compound (210 mg; 0.48 mmol) using the same procedure as described in the second synthetic route for the preparation of Example 193 compound.

15 [M + H]<sup>+</sup> = 506.6

[α] (8.8 mg/2 mL) MeOH<sup>589</sup> = +33.93

#### Example 195



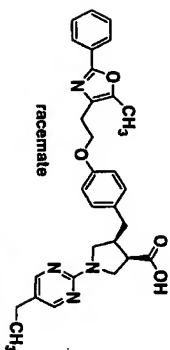
20

The title compound (34 mg; 51%) was prepared from Example 180 Part A compound (50 mg; 0.12 mmol) and 2-chloro-5-bromopyrimidine (100 mg) using the 2-step procedure employed in the synthesis of Example 164.

25 [M + H]<sup>+</sup> = 563.2

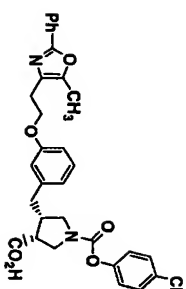
30

- 293 -

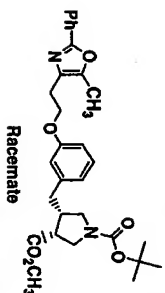
Example 196

The title compound (31 mg; 51%) was prepared from

Example 180 Part A compound (50 mg; 0.12 mmol) with 2-chloro-5-ethylpyrimidine (100 mg) using the same 2-step procedure as employed in the synthesis of Example 164.  $[M + H]^+ = 513.3$

Example 1973R, 4S Enantiomer

15 A.

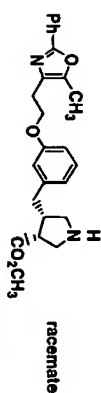


To a mixture of Example 32 Part F compound (1.66

g; 4.9 mmol) and 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethanol (1.11 g, 5.4 mmol) in toluene (40 mL) was added cyanomethylenetriethylphosphine (3.58 g; 14.8 mmol) dropwise. The mixture was heated at 80°C for 3 h, cooled to RT, concentrated in vacuo and partitioned between

EtOAc and water. The organic phase was washed with water (2x) and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; stepwise gradient from hexane to hex:EtOAc 2:3) to give Part A compound (2.44 g; 95%) as an oil.

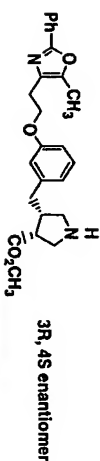
B.



10 A solution of Part A compound (2.34 g; 4.49 mmol)

and 4M HCl in dioxane (50 mL) in  $\text{CH}_2\text{Cl}_2$  (50 mL) was stirred at RT for 4.5 h, then concentrated in vacuo and partitioned between EtOAc and saturated aqueous  $\text{NaHCO}_3$ . The organic layer was washed with saturated aqueous  $\text{NaHCO}_3$  (2X), water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give Part B compound (1.72 g; 91%) as an orange oil.

C.

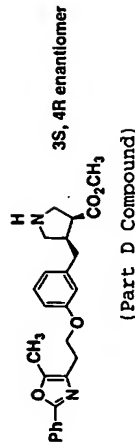
3R, 4S enantiomer

The individual enantiomers of Part B compound were separated by preparative HPLC using a CHIRALCEL OD column from Chiral Technologies Inc (5 cm ID X 50 cm, 20  $\mu$ ): flow rate = 45 mL/min; isocratic conditions = 80:20 A:B, where A = heptane + 0.1%  $\text{Et}_3\text{NH}$ ; B = iPrOH + 0.1%  $\text{Et}_3\text{NH}$ ; detector wavelength = 279 nm. The first fraction from the chiral preparative HPLC was identified as the desired 3R, 4S enantiomer (760 mg; Part C compound). Chiral analytical HPLC using a Daicel Chiralcel OD 4.6 x 500 mm column: flow rate = 1 mL/min; isocratic conditions = 80:20 A:B, where A = heptane + 0.1%  $\text{Et}_3\text{NH}$ ; B = IPA + 0.1%



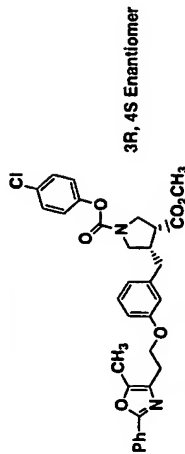
Et<sub>3</sub>NH; detector wavelength = 279 nm; retention time = 21 min. Optical rotation = +13.36°

The second (slower-eluting) fraction (660 mg) from the chiral prep HPLC separation was identified as the opposite enantiomer (Part D compound). Chiral analytical HPLC (same conditions as above) retention time = 29 min. Optical rotation = -13.60°



10

E.

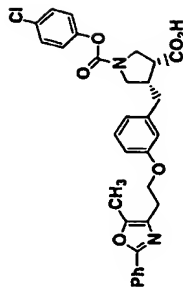


15

To a 0°C solution of Part C 3R, 4S enantiomer (10.0 mg; 0.0238 mmol) and aqueous saturated NaHCO<sub>3</sub> (0.50 mL) in THF (0.50 mL) was added 4-chlorophenyl chloroformate (4.0 μL; 0.0286 mmol). The reaction was stirred at 0°C for 30 min, then was allowed to warm to RT and stirred overnight at RT. Volatiles were removed in vacuo, and the residue was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc (2X). The combined organic extracts were washed with water (1X) and brine (1X), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give Part E compound, which was used in the next reaction without further purification.

30

F.



3R, 4S Enantiomer

A solution of Part E compound in HOAc (0.80 mL) and concentrated HCl (0.20 mL) was shaken at 70°C for 6.5 h, then cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (YMC Combiprep ODS-A 30 X 50 mm column; flow rate = 35 mL/min; 8 min continuous gradient from 20:80 B:A to 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give the title compound (6.3 mg; 47%).  
[M + H]<sup>+</sup> = 561.23

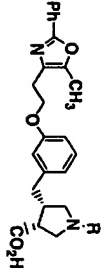
15

Examples 198-219

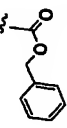
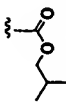
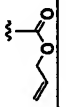


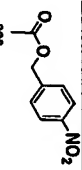
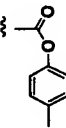
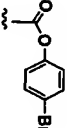
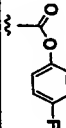
Examples 198 through 219 were prepared in a similar fashion to Example 197 (from Example 197 Part C compound) using appropriate chloroformates.

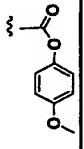
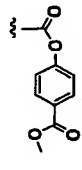
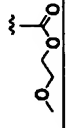

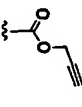

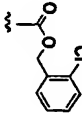

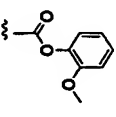
20

25



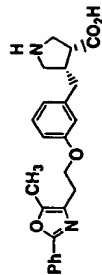
3R,4S Enantiomer

Example #	R	[M + H] <sup>+</sup>
198		541.3
199		507.33
200		491.28
201		493.3
202		507.33
203		586.27
204		541.3
205		605.21
206		545.27

Example #	R	[M + H] <sup>+</sup>
207		557.28
208		585.27
209		509.31
210		493.29
211		489.26
212		521.34
213		575.25
214		497.27
215		557.28

desired 3R,4S enantiomer shown above was obtained (140 mg; chiral analytical HPLC retention time = 16 min).

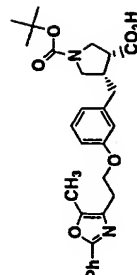
B.



3R, 4S Enantiomer

A solution of chiral Part A compound (10 mg; 0.0230 mmol) in HOAc (800  $\mu$ L) and concentrated HCl (200  $\mu$ L) was shaken at 70°C overnight. Concentration of the reaction solution in vacuo yielded the pure title compound (10.1 mg; 94%).  
 $[M + H]^+ = 407.44$

Example 221

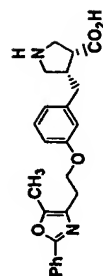


3R, 4S Enantiomer

To a 0°C solution of Example 220 (6.1 mg; 0.015 mmol) in saturated aqueous NaHCO<sub>3</sub> (0.50 mL) and THF (0.50 mL) was added di-tert-butyl dicarbonate (4 mg; 0.017 mmol). The reaction was stirred at 0°C for 10 min, then was allowed to warm to RT and stirred at RT for 2.5 h. Volatiles were removed in vacuo; water and EtOAc were added. The mixture was cooled to 0°C and the aqueous phase was acidified to pH 1 with saturated aqueous H<sub>2</sub>SO<sub>4</sub> and extracted with EtOAc (2X). The combined organic extracts were washed with water (2X) and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was

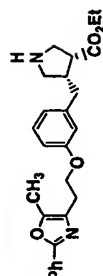
Example #	R	$[M + H]^+$
216		561.22
217		569.21
218		513.22
219		465.29

Example 220



3R, 4S Enantiomer

A.

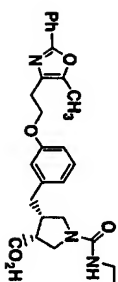


3R, 4S Enantiomer

The racemic Example 21 Part C compound (970 mg) was purified by chiral preparative HPLC using the same conditions as described in Example 197 Part C. The

purified by preparative HPLC (as described for Example 197 Part F) to yield the title compound (3.2 mg, 42%).  
 $[M + H]^+ = 507.30$

### 5 Example 222

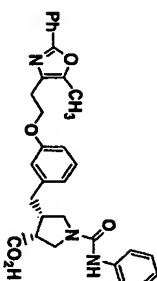


**3R,4S Enantiomer**

- 10 To a solution of Example 220 (9.3 mg; 0.023 mmol) in THF (250  $\mu$ L) and saturated aqueous  $\text{NaHCO}_3$  (250  $\mu$ L) was added ethyl isocyanate (2.18  $\mu$ L; 0.0276 mmol) at RT. The reaction was stirred at RT overnight. More ethyl isocyanate (2.2  $\mu$ L) was added to drive the reaction to completion (6 h), after which volatiles were removed in vacuo. The residue was dissolved in water, cooled to 0°C and acidified to pH 1 with saturated aqueous  $\text{KHSO}_4$ . A white precipitate formed. The aqueous phase was extracted with EtOAc (3X). The combined organic extracts were washed with water (2X) and brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The residue was purified by preparative HPLC (Phenomenex Luna 5 $\mu$  21.2 X 100mm column; flow rate = 20 mL/min; 10 min continuous gradient from 20:80 B:A to 100% B, where solvent A = 90:10:0.1  $\text{H}_2\text{O}$ :MeOH:TFA and solvent B = 90:10:0.1 MeOH: $\text{H}_2\text{O}$ :TFA) to give the title compound (9.6 mg; 87%).  
 $[M + H]^+ = 478.49$

30

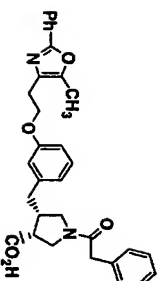
### Example 223



**3R,4S Enantiomer**

- 5 To a solution of Example 220 (9.3 mg; 0.023 mmol) in THF (250  $\mu$ L) and saturated aqueous  $\text{NaHCO}_3$  (250  $\mu$ L) was added phenyl isocyanate (3.75  $\mu$ L; 0.0345 mmol) at RT. The reaction was stirred at room temperature overnight and then concentrated down. The solid residue was redissolved into water, cooled in an ice bath, and acidified to pH 1.0 with saturated aqueous  $\text{KHSO}_4$ . This acidic solution was extracted with EtOAc (3X). The combined extracts were washed with water (2X) and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The product was purified by preparative HPLC (as described for Example 222) to yield the title compound (9.1 mg; 75%).  
 $[M + H]^+ = 526.49$

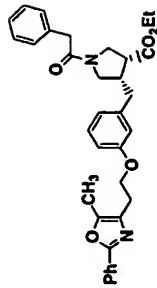
### Example 224



**3R,4S Enantiomer**

25

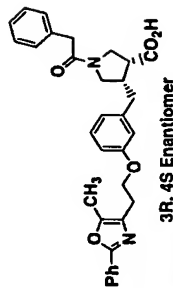
A.



3R, 4S Enantiomer

To a solution of Example 220 Part A compound (10 mg; 0.0230 mmol) in  $\text{CH}_2\text{Cl}_2$  (500  $\mu\text{L}$ ) was added TEA (4.8  $\mu\text{L}$ ; 0.035 mmol) and phenylacetyl chloride (3.7  $\mu\text{L}$ ; 0.028 mmol). The reaction was stirred at RT for 3 h, then was concentrated in vacuo. The residue was partitioned between EtOAc and water; the organic phase was washed with water (2X) and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give Part A compound (12.5 mg) as a yellow oil, which was used in the next step without further purification.

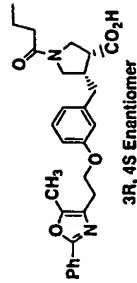
15 B.



A solution of Part A compound in HOAc (800  $\mu\text{L}$ ) and concentrated HCl (200  $\mu\text{L}$ ). The reaction was shaken at 70°C for 13.5 h, then cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 222) to yield the title compound (5.0 mg; 41%) as a solid.  
 $[\text{M} + \text{H}]^+ = 525.50$ .

25

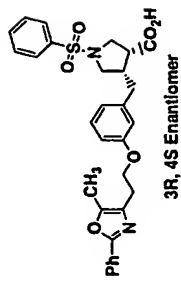
Example 225



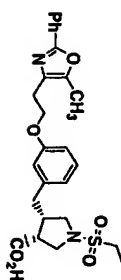
Example 225 (7.1 mg; 65%) was synthesized employing the procedure described in Example 224, except that butyryl chloride was used in the sequence instead of phenylacetyl chloride.  $[\text{M} + \text{H}]^+ = 477.50$ .

10

Example 226

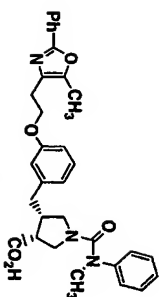


A solution of Example 220 (9.3 mg; 0.023 mmol) and phenylsulfonfyl chloride (4.4  $\mu\text{L}$ ; 0.035 mmol) in THF (250  $\mu\text{L}$ ) and saturated aqueous  $\text{NaHCO}_3$  (250  $\mu\text{L}$ ) was stirred at RT for 3.5 h, then was concentrated in vacuo. The residue was taken up in water, cooled to 0°C, and acidified to pH 1 with saturated aqueous  $\text{KHSO}_4$  (precipitate formation). The mixture was extracted with EtOAc (3X). The combined organic extracts were washed with water (2X) and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 222) to yield the title compound (8.1 mg; 64%).  $[\text{M} + \text{H}]^+ = 547.46$ .

Example 2273R, 4S Enantiomer

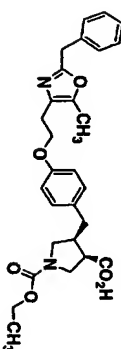
5 Example 227 (4.4 mg; 38%) was synthesized employing the procedure described in Example 226, except that ethane sulfonyl chloride was used in the sequence instead of phenyl sulfonyl chloride.  $[M + H]^+ = 499.46$

10

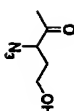
Example 2283R, 4S Enantiomer

15 To a RT solution of Example 220 (9.3 mg; 0.023 mmol) in THF (250  $\mu$ L) and saturated aqueous  $\text{NaHCO}_3$  (250  $\mu$ L) was added N-methyl-N-phenylcarbamoyl chloride (4.7 mg; 0.028 mmol). The reaction was stirred at RT for 3.5 h, then was concentrated in vacuo. The residue was dissolved into water, cooled to  $0^\circ\text{C}$ , and acidified to pH 1.0 with saturated aqueous  $\text{KHSO}_4$  (precipitate formation). The mixture was extracted with  $\text{EtOAc}$  (3X). The combined organic extracts were washed with water (2X) and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The product was purified by preparative HPLC (as described for Example 222) to yield the title compound (6.5 mg; 52%) as a solid.

25  $[M + H]^+ = 540.24$

Example 229

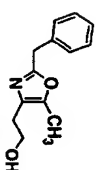
5 A.



A mixture of 3-chloro-5-hydroxy-2-pentanone (5 g; 36.7 mmol) and sodium azide (4.8 g; 73.8 mmol) in acetone (100 mL) and  $\text{H}_2\text{O}$  (~30 mL) was stirred at  $50^\circ\text{C}$  for 2.5 h. The reaction was cooled to RT and the acetone was removed in vacuo. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ ; the combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 100% hex to 100%  $\text{EtOAc}$ ) to give Part A compound (4.38 g; 82%).

15

B.



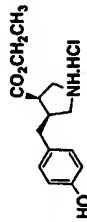
20 A mixture of Part A compound (500 mg; 3.50 mmol) and resin-bound PhP (1.50 g of 3 mmol/g resin; 4.50 mmol) in dioxane (20 mL) was shaken for 10 min at RT. Phenylacetyl chloride (1 g; 6.50 mmol) was added and the reaction was heated at  $80^\circ\text{C}$  for 18 h, then cooled to RT and filtered. A mixture of the filtrate in MeOH (20 mL) and aqueous LiOH (6 mL of a 2N solution) was shaken at  $70^\circ\text{C}$  for 15 min, and more aqueous LiOH 2N was added until the pH of the solution remained at 9. The mixture was concentrated in vacuo and partitioned between water and  $\text{CH}_2\text{Cl}_2$ ; the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The

30

combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 20% hex/ EtOAc to 100% EtOAc) to give Part B compound (140 mg; 19%) as a pale yellow oil.

[M + H]<sup>+</sup> = 218; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.31 (m, 5 H), 4.03 (s, 2 H), 3.87 (t, J = 6.0 Hz, 2 H), 2.64 (t, J = 6.0 Hz, 2 H) 2.19 (s, 3 H).

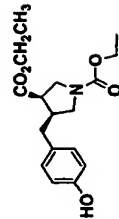
10 C.



A mixture of Example 23 Part D compound (4.8 g; 10 mmol) and 10% Pd/C (500 mg) in HOAc (100 mL) was stirred under an atmosphere of H<sub>2</sub> (60 psi) for 18 h. The catalyst was filtered off on Celite® and the filtrate was concentrated in vacuo. The residue was azeotroped with toluene, then was treated with 1N HCl in dioxane (50 mL) for 10 min. and concentrated in vacuo to afford Part C compound (3.3g; 95%) as an orange oil which was used in the next step without further purification.

[M + H]<sup>+</sup> = 250.11

D.

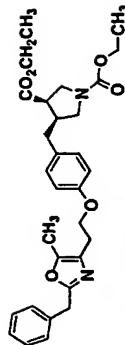


To a mixture of part C compound (300 mg, 1.05 mmol) in THF (3 mL) and saturated aqueous Na<sub>2</sub>CO<sub>3</sub> (5 mL) was added ethyl chloroformate (120 μL, 1.30 mmol), and the reaction was stirred overnight at RT. The THF was removed in vacuo and the aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>; the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was

chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to give Part D compound (110 mg; 32%).

[M + H]<sup>+</sup> = 322.18

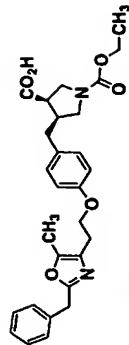
5 E.



A mixture of Part D compound (13 mg, 40 μmol), part B compound (10.3 mg, 48 μmol), cyanomethylene tributylphosphine (30 μL, 120 μmol) in toluene (0.5 mL) was heated at 70°C for 18h. The mixture was concentrated in vacuo and the resulting residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 60% EtOAc) to give part E compound as an oil. ([M + H]<sup>+</sup> = 521.24)

15

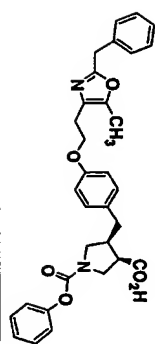
F.



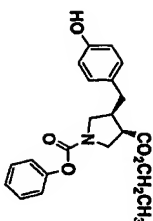
A solution of Part E compound in 25% concentrated HCl in HOAc (1 mL) was heated at 70°C for 8h. Volatiles were removed in vacuo and the residue was purified by HPLC (as described for Example 1) and lyophilized (water with 2-4% methanol) to give the title compound (5.0 mg; 26% over 2 steps) as a white solid.

25 [M + H]<sup>+</sup> = 493.20

30

Example 230

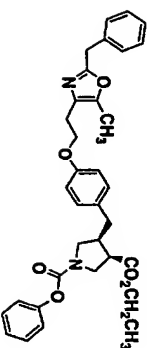
A.



To a mixture of Example 229 part C compound (300 mg, 1.05 mmol), THF (3 mL) and saturated aqueous  $\text{Na}_2\text{CO}_3$  (5 mL) was added phenyl chloroformate (160  $\mu\text{L}$ , 1.30 mmol). The reaction was stirred overnight at RT, after which the THF was removed in vacuo and the resulting aqueous solution was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 100% hex to 100% EtOAc) to give Part A compound (140 mg; 36%) as a colorless oil.

$[\text{M} + \text{H}]^+ = 370.14$

B.



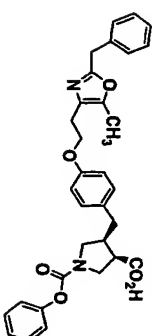
A mixture of Part A compound (15 mg, 40  $\mu\text{mol}$ ), Example 229 part B compound (10.3 mg, 48  $\mu\text{mol}$ ), cyanomethylene tributylphosphine (30  $\mu\text{L}$ , 120  $\mu\text{mol}$ ) in toluene (0.5 mL) was heated at  $70^\circ\text{C}$  for 18h. Volatiles were removed in vacuo and the residue was chromatographed

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( $\text{SiO}_2$ ; continuous gradient from 100% hexane to 60:4 hex:EtOAc) to give Part B compound as an oil.

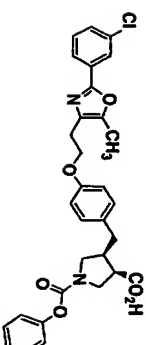
$[\text{M} + \text{H}]^+ = 569.18$

C.

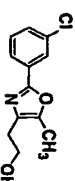


A solution of Part B compound in 25% concentrated HCl in HOAc (1 mL) was heated at  $70^\circ\text{C}$  for 20 h. The mixture was concentrated in vacuo and the residue was purified by preparative HPLC (as described for Example 1) and lyophilized (water with 2-4% methanol) to give the title compound (10.5 mg; 48% over 2 steps) as a white solid.

$[\text{M} + \text{H}]^+ = 541.18$

Example 231

A.



A mixture of example 229 part A compound (500 mg; 3.50 mmol) and resin-bound Ph<sub>3</sub>P (1.50 g of 3 mmol/g resin; 4.50 mmol) in dioxane (20 mL) was shaken for 10 min at RT. 3-chlorobenzoyl chloride (1.22 g; 6.50 mmol) was then added and the reaction was heated at  $80^\circ\text{C}$  for 18 h, then cooled to RT, filtered and concentrated in vacuo.

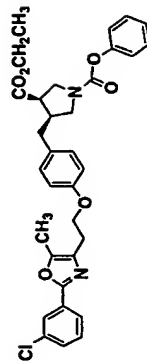
- 311 -



The residue was dissolved in MeOH (10 mL) and THF (10 mL) and aqueous LiOH (6 mL of a 2N solution) was added. The mixture was shaken at 50°C and more aqueous LiOH was added until the pH of the solution remained constant at

- 5 9. The mixture was then heated at 50°C for 6h, cooled to RT and concentrated. The residue was partitioned between H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub>; the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 20% hex/EtOAc to 100% EtOAc) to give Part A compound (80 mg; 9%).  
[M + H]<sup>+</sup> = 260.36;

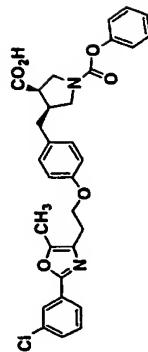
B.



15

- A mixture of Example 230 part A compound (15 mg, 40 μmol), part A compound (11.4 mg, 48 μmol) and cyanomethylene tributylphosphine (30 μL, 120 μmol) in toluene (0.5 mL) was heated at 70°C for 18h. The mixture was concentrated in vacuo and the resulting residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 60:40 EtOAc) to give Part B compound.  
[M + H]<sup>+</sup> = 589.44

25 C.



- A solution of Part B compound in concentrated HCl/HOAc (1 mL of a 1:3 mixture) was heated at 70°C for 18h. The mixture was concentrated in vacuo and the residue was purified by preparative HPLC (as described

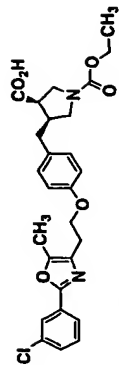
- 312 -

for Example 1) and lyophilized (water with 2-4% methanol) to give the title compound (5.6 mg; 25% for 2 steps) as a white solid.

[M + H]<sup>+</sup> = 561.63

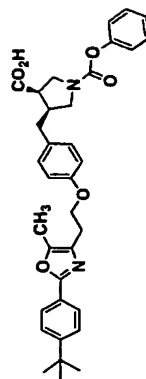
5

### Example 232

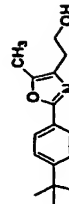


- A mixture of example 229 part D compound (13 mg, 40 μmol), example 231 part A compound (11.4 mg, 48 μmol) and cyanomethylene tributylphosphine (30 μL, 120 μmol) in toluene (0.5 mL) was heated at 70°C for 18h. The mixture was concentrated in vacuo and the resulting residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 60% EtOAc) to give the ethyl ester of part E compound ([M + H]<sup>+</sup> = 541.46). This ester was dissolved in 25% concentrated HCl in acetic acid (1 mL) and heated at 70°C for 18h. The mixture was concentrated and the residue was purified by HPLC (as described for Example 1) and lyophilized (water with 2-4% methanol) to give the title compound (3.5 mg; 18%) as a white solid.  
[M + H]<sup>+</sup> = 513.54

### Example 233



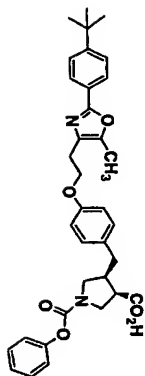
A.



- 313 -

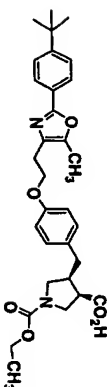
Part A compound was synthesized according to the general procedure described for the synthesis of Example 231 Part A compound except that 4-tert-butylbenzoyl chloride was used instead of 3-chlorobenzoyl chloride.

B.



The title compound (11 mg; 50%) was prepared from Part A compound and Example 230 part A compound (15 mg; 40  $\mu$ mol) using the same sequence as for Example 231 except that 4-tert-butylbenzoyl chloride (1.37 g; 6.50 mmol) was used instead of 3-chlorobenzoyl chloride.  $[M + H]^+ = 583.64$

#### Example 234

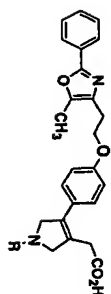


The title compound (7 mg; 30%) was prepared from example 229 part D compound (13 mg, 40  $\mu$ M), using the same sequence as for Example 232 except that 4-tert-butylbenzoyl chloride (1.37 g; 6.50 mmol) was used instead of 3-chlorobenzoyl chloride.

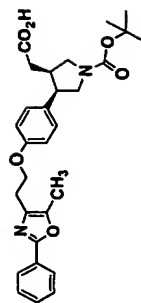
$[M + H]^+ = 535.64$

#### Examples 235-241

Examples 235-241 of the invention were prepared in a similar fashion to Example 43 (from Example 43 Part D compound) using a variety of chloroformates.

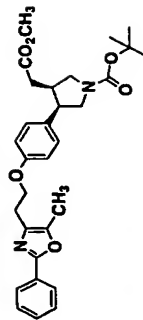


Example #	R	$[M + H]^+$
235		491.1
236		491.1
237		505.1
238		505.1
239		539.0
240		525.0
241		555.0

Example 242

5

A.

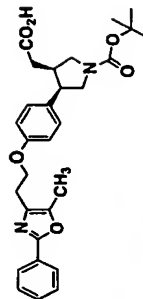


A mixture of Example 43, part C compound (105 mg; 0.202 mmol) and 10% Pd/C (75 mg) in MeOH/HOAc (3 mL of a 1:1 solution) was stirred at RT under an atmosphere of H<sub>2</sub> (75 psi) for 48 h. The catalyst was filtered off on Celite® and the filtrate was concentrated in vacuo to give Part A compound (85 mg; 81%).

[M + H]<sup>+</sup> = 521.5

15

B.

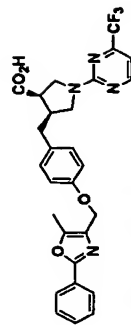


A mixture of Part A compound (10 mg; 0.019 mmol) and LiOH·H<sub>2</sub>O (8 mg; 0.19 mmol) in THF/H<sub>2</sub>O (1 mL of a 1:1 solution) was stirred at RT for 16 h, after which the pH was adjusted to ~5 with aqueous 1 M HCl. The mixture was extracted with EtOAc (2 mL). The organic phase was concentrated in vacuo and the residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; flow rate = 20 mL/min; 10 min continuous gradient

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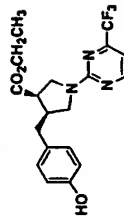
from 30:70 B:A to 100% B + 5 min hold-time at 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA. The product was further chromatographed (SiO<sub>2</sub>, EtOAc) to give the title compound

5 (2.3 mg; 24%) as a colourless oil.

[M + H]<sup>+</sup> = 507.1Example 243

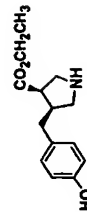
10

A.



A mixture of Example 229 Part C compound (920 mg; 3.69 mmol)

15

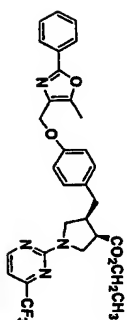


and 2-chloro-4-(trifluoromethyl)pyrimidine (0.53 mL; 4.43 mmol) and Et<sub>3</sub>N (1.03 mL; 7.38 mmol) in toluene (12.3 mL) was stirred at 80°C for 2 h, after which the reaction was partitioned between EtOAc (65 mL) and aqueous 1 M HCl (25 mL). The organic phase was washed with H<sub>2</sub>O (2 x 65 mL) and brine (70 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 90% hex to 100% EtOAc) to give Part A compound (918 mg; 63%) as a colorless oil.

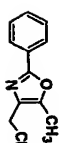
B.

25

- 317 -

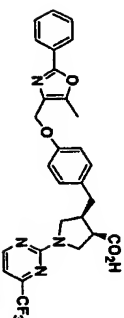


A mixture of 4-chloromethyl-5-methyl-2-phenylloxazole (12.6 mg; 0.0608 mmol),



Part A compound (12 mg; 0.0304 mmol) and  $K_2CO_3$  (8.4 mg; 0.0608 mmol) in  $CH_3CN$  (1 mL) was stirred at 70°C for 15 h, after which the reaction was partitioned between EtOAc (10 mL) and  $H_2O$  (5 mL). The organic phase was washed with brine (20 mL), dried ( $MgSO_4$ ) and concentrated in vacuo to provide crude Part B compound as an oil, which was used in the next step without further purification.

C.



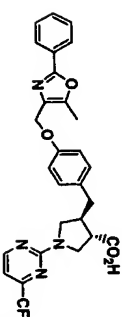
A solution of Part B compound  $LiOH \cdot H_2O$  (5.1 mg) in THF (1 mL) and  $H_2O$  (0.5 mL) was stirred at RT for 16 h and then heated to 70°C for an additional 6 h, after which the reaction mixture was cooled to RT and the pH was adjusted to ~2 with aqueous 1 N HCl. The mixture was partitioned between EtOAc (10 mL) and  $H_2O$  (5 mL). The organic phase was washed with brine (20 mL), dried ( $MgSO_4$ ) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30 : 70 Solvent A: Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give two compounds. The compound

with the shorter retention time on HPLC was lyophilized from 1,4-dioxane to give the title compound (1.8 mg; 11% for two steps) as a white solid.

$[M + H]^+ = 539.0$

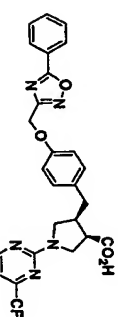
The second compound (longer retention time) was determined to be the corresponding epimerized trans-isomer of Example 243. This compound was also lyophilized from 1,4-dioxane to give Example 244 (1.1 mg; 6.7% for 2 steps) as a white solid.

#### Example 244

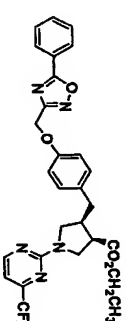


$[M + H]^+ = 539.0$

#### Example 245



A.

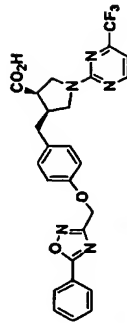


A mixture of Example 25 Part C compound (11.8 mg; 0.0608 mmol), Example 243 Part A compound (12 mg; 0.0304 mmol) and  $K_2CO_3$  (8.4 mg; 0.0608 mmol) in  $CH_3CN$  (1 mL) was stirred at 70°C for 15 h, then was cooled to RT and partitioned between EtOAc (10 mL) and  $H_2O$  (5 mL). The

organic phase was washed with brine (20 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to provide crude Part A compound as an oil, which was used in the next step without further purification.

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৯.



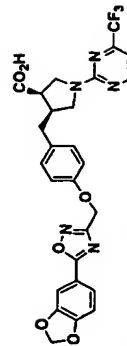
A solution of crude Part A compound in HOAc/

concentrated HCl (1.2 mL of a 9:1 solution) was stirred at 70°C for 17 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30 : 70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give the title compound (2.0 mg; 13% for 2 steps) as a white solid.

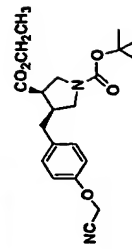
$$[\text{M} + \text{H}]^+ = 526.0$$

20

### Example 246



A.



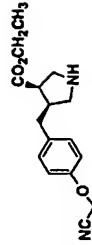
25

A mixture of Example 23 Part E compound (640 mg; 1.83 mmol),  $\alpha$ -chloroacetoneitrile (0.232 mL; 3.66 mmol)

and  $K_2CO_3$  (506 mg; 3.66 mmol) in  $CH_3CN$  (9.2 mL) at  $70^\circ C$  was stirred for 18 h, then was cooled to RT and partitioned between EtOAc (150 mL) and  $H_2O$  (80 mL). The organic phase was washed with brine (20 mL), dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; continuous gradient from 100% hex to 100% EtOAc over 55 min) to give Part A compound (590 mg; 83%) as an oil.

10

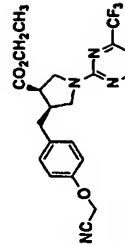
B.



A solution of Part A compound (590 mg; 1.52 mmol) and HCl (0.76 mL of a 4 M solution in dioxane) in  $\text{CH}_2\text{Cl}_2$  (4 mL) was stirred at RT for 3 h, then was concentrated in vacuo to give crude Part B compound (355 mg; 81%) as an oil.

20

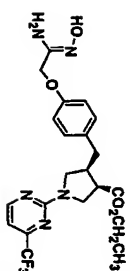
٧



A mixture of Part B compound (355 mg; 1.23 mmol) and 2-chloro-4-(trifluoromethyl)pyrimidine (0.298 mL; 2.47 mmol) and Et<sub>3</sub>N (0.344 mL; 2.47 mmol) in toluene (5 mL) was stirred at 80°C for 2 h, after which the reaction was partitioned between EtOAc (35 mL) and aqueous 1 M HCl (15 mL). The organic phase was washed with H<sub>2</sub>O (2 x 35 mL) and brine (40 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous

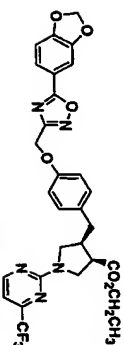
gradient from 90% hex to 100% EtOAc) to give Part C compound (246 mg; 46%) as a colorless oil.

D.



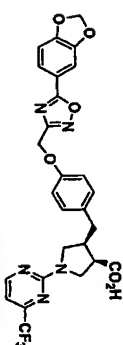
A mixture of Part C compound (246 mg; 0.567 mmol) and hydroxylamine (112 mg of a 50% solution in water; 1.70 mmol) in MeOH:H<sub>2</sub>O (6 mL of a 2:1 solution) was heated to reflux for 5 h, after which volatiles were removed in vacuo. The residue was partitioned between EtOAc (30 mL) and H<sub>2</sub>O (15 mL). The organic phase was washed with brine (40 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to provide crude Part D compound (208 mg, 79%) as an oil.

•



A mixture of Part D compound (30 mg; 0.0642 mmol), piperonylpyl chloride (23.6 mg; 0.128 mmol) in toluene (1 mL) was shaken at 115°C for 6 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30 : 70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give the title compound (14 mg, 37%) as an oil.

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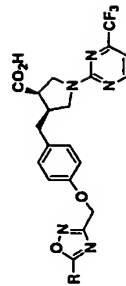
A solution of Part E compound (14 mg; 0.0235 mmol) in HOAc/concentrated HCl (1.5 mL of a 9:1 solution) was stirred at 70°C for 17 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30 : 70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give the title compound (6.4 mg; 48%) as a white solid.

$[M + H]^+ = 570.0$

15

### Examples 247-250

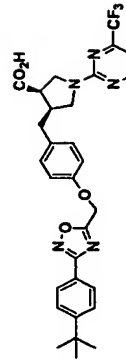
Example 247 through 250 were prepared in a similar fashion to Example 246 (from Example 246 part D compound) using a variety of acid chlorides.



Example #	R	[M + H] <sup>+</sup>
247		582.0
248		602.1
249		609.9
250		570.4

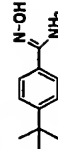
5

## Example 251



A.

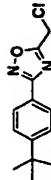
10



A mixture of 4-tert-butyl-benzonitrile (5.0 g; 31.4 mmol), hydroxylamine hydrochloride (3.27 g; 47.1 mmol) and K<sub>2</sub>CO<sub>3</sub> (8.68 g; 62.8 mmol) in EtOH (170 mL) was stirred at reflux for 18 h, then was cooled to RT and filtered.

5 The filtrate was concentrated in vacuo to provide crude Part A compound as a solid, which was used in the next step without further purification

B.

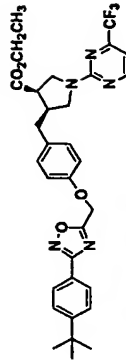


10

To a solution of crude Part A compound in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) at RT was added α-chloroacetyl chloride (2.97 mL; 37.3 mmol) followed by Et<sub>3</sub>N (5.2 mL; 37.3 mmol). The reaction mixture was stirred at RT for 2 h, after which volatiles were removed in vacuo and the residue was dissolved in toluene (80 mL). The reaction mixture was then heated at reflux for 12 h, then was cooled to RT and partitioned between EtOAc (150 mL) and H<sub>2</sub>O (100 mL). The organic phase was washed with brine (200 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to give Part B compound (746 mg; 9.5% for 2 steps) as a solid.

25

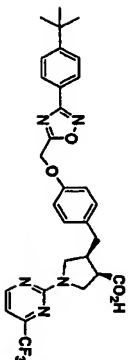
C.



A mixture of Part B compound (25.5 mg; 0.102 mmol), Example 243 Part A compound (20 mg; 0.051 mmol) and K<sub>2</sub>CO<sub>3</sub> (14.1 mg; 0.102 mmol) in CH<sub>3</sub>CN (1.2 mL) was stirred at 90°C for 14 h, after which the reaction was partitioned between EtOAc (10 mL) and H<sub>2</sub>O (5 mL). The organic phase was washed with brine (20 mL), dried (MgSO<sub>4</sub>) and

concentrated in vacuo to provide crude Part B compound as an oil, which was used in the next step without further purification.

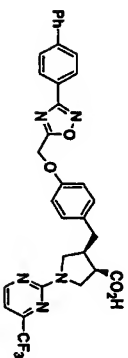
5 D.



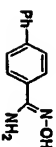
A solution of Part C compound in HOAc/concentrated HCl (1.2 mL of a 9:1 solution) was stirred at 70°C for 17 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30 : 70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give the title compound (10.4 mg; 35%).

$[M + H]^+ = 582.0$

#### Example 252



A.



A mixture of 4-biphenylcarbonitrile (5.0 g; 27.9 mmol), hydroxylamine hydrochloride (2.9 g; 41.8 mmol) and  $K_2CO_3$  (7.7 g; 55.8 mmol) in EtOH (150 mL) was stirred at reflux for 18 h, then was cooled to RT and filtered. The filtrate was concentrated in vacuo to provide crude Part

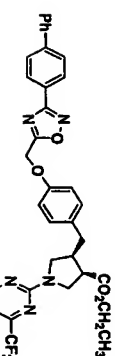
A compound as a solid, which was used in the next step without further purification

B.



To a solution of crude Part A compound in  $CH_2Cl_2$  (50 mL) at RT was added  $\alpha$ -chloroacetyl chloride (2.7 mL; 33.5 mmol) followed by Et<sub>3</sub>N (4.7 mL; 33.5 mmol). The reaction mixture was stirred at RT for 2 h, after which volatiles were removed in vacuo and the residue was dissolved in toluene (80 mL). The reaction mixture was then heated and stirred at reflux for 13 h, after which the mixture was cooled to RT. The reaction was then partitioned between EtOAc (150 mL) and H<sub>2</sub>O (100 mL). The organic phase was washed with brine (200 mL), dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; continuous gradient from 100% hex to 100% EtOAc) to give Part B compound (431 mg; 5.7% for 2 steps) as a solid.

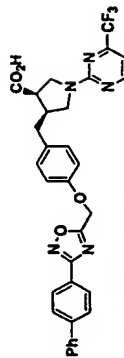
C.



A mixture of Part B compound (27.5 mg; 0.102 mmol), Example 243 Part A compound (20 mg; 0.051 mmol) and  $K_2CO_3$  (14.1 mg; 0.102 mmol) in  $CH_3CN$  (1.2 mL) was stirred at 90°C for 14 h, then was cooled to RT and partitioned between EtOAc (10 mL) and H<sub>2</sub>O (5 mL). The organic phase was washed with brine (20 mL), dried ( $MgSO_4$ ) and concentrated in vacuo to provide crude Part B compound as an oil, which was used in the next step without further purification.



D.

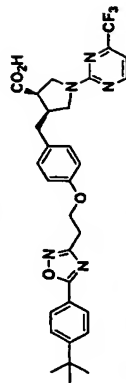


A solution of Part C compound in HOAc/concentrated HCl (1.2 mL of a 9:1 solution) was stirred at 70°C for 17 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30 : 70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give the title compound (4.1 mg; 13%) as a white solid.

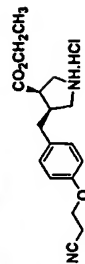
$$[M + H]^+ = 602.0$$

#### Example 253

15



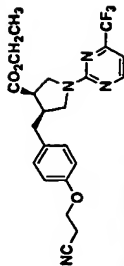
A.



20

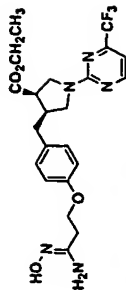
A solution of Example 51 Part B compound (329 mg; 0.82 mmol) and HCl (0.41 mL of a 4 M solution in dioxane; 1.64 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was stirred at RT for 3 h, then was concentrated in vacuo to give crude Part A compound (188 mg; 76%) as an oil.

B.



A mixture of crude Part A compound (188 mg; 0.623 mmol) and 2-chloro-4-(trifluoromethyl)pyrimidine (0.150 mL; 1.25 mmol) and Et<sub>3</sub>N (0.175 mL; 1.25 mmol) in toluene (6.2 mL) was stirred at 80°C for 2 h, then was cooled to RT and partitioned between EtOAc (35 mL) and aqueous 1 M HCl (15 mL). The organic phase was washed with H<sub>2</sub>O (2 x 35 mL) and brine (40 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 90% hex to 100% EtOAc) to give Part B compound (170 mg; 61%) as a colorless oil.

15 C.



A mixture of Part B compound (170 mg; 0.379 mmol)

and hydroxylamine (75 mg of a 50% solution in water;

1.138 mmol) in MeOH:H<sub>2</sub>O (5 mL of a 2:1 solution) was

heated at reflux for 5 h, then was cooled to RT and

concentrated in vacuo. The residue was partitioned

between EtOAc (30 mL) and H<sub>2</sub>O (15 mL). The organic phase

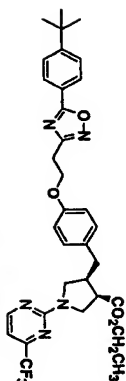
was washed with brine (40 mL), dried (MgSO<sub>4</sub>) and

concentrated in vacuo to provide crude Part C compound

(149 mg, 82%) as an oil.

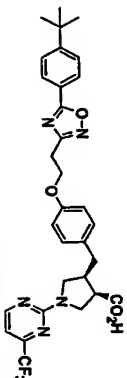
30

D.



- A mixture of Part C compound (28 mg; 0.0582 mmol), 4-tert-butylbenzoyl chloride (22.8 mg; 0.116 mmol) in toluene (1 mL) was shaken at 115°C for 6 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30 : 70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give Part D compound (22 mg, 61%) as an oil.

E.

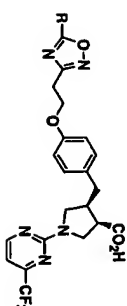


- A solution of Part D compound (22 mg; 0.0353 mmol) in HOAc/concentrated HCl (1.3 mL of a 9:1 solution) was stirred at 70°C for 16 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30 : 70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give the title compound (10.8 mg; 51%) as a white solid.
- [M + H]<sup>+</sup> = 596.5

30

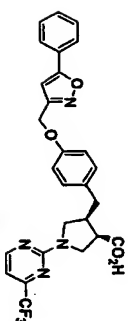
Examples 254-255

- Examples 254-255 of the invention were prepared in a similar fashion to Example 253 (from Example 253 part C compound) using a variety of acid chlorides.



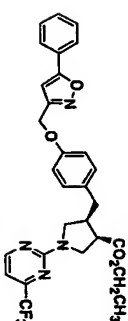
Example #	R	[M + H] <sup>+</sup>
254		570.1
255		574.1

10

Example 256

15

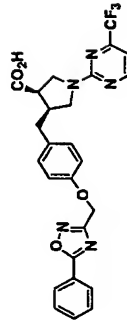
A.



A mixture of 4-chloromethyl-5-phenylisoxazole (14.7 mg; 0.076 mmol), Example 243 Part A compound (15 mg; 0.038 mmol) and K<sub>2</sub>CO<sub>3</sub> (10.5 mg; 0.076 mmol) in CH<sub>3</sub>CN (1 mL) was heated at 90°C for 16 h, after which the reaction was partitioned between EtOAc (10 mL) and H<sub>2</sub>O (5 mL). The organic phase was washed with brine (20 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to provide crude Part A compound as an oil, which was used in the next step without further purification.

10

B.

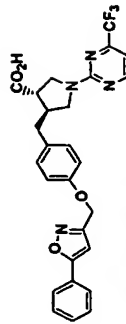


A solution of Part A compound and LiOH·H<sub>2</sub>O (8.0 mg; 0.19 mmol) in THF (1.2 mL) and H<sub>2</sub>O (0.6 mL) was stirred at 60°C for 12 h, then was cooled to RT and the pH was adjusted to ~2 with aqueous 1 N HCl. The mixture was partitioned between EtOAc (10 mL) and H<sub>2</sub>O (5 mL). The organic phase was washed with brine (20 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30 : 70 Solvent A: Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give two compounds. The compound with the shorter retention time was lyophilized from 1,4-dioxane to give the title compound (8.1 mg; 41% for 2 steps) as a white solid.

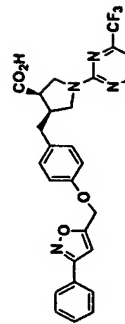
[M + H]<sup>+</sup> = 525.3

The second compound (longer retention time) was determined to be the corresponding epimerized trans-isomer of Example 256. This compound was also lyophilized from 1,4-dioxane to give Example 257 (1.1 mg; 5.5% for steps) as a white solid.

- 332 -

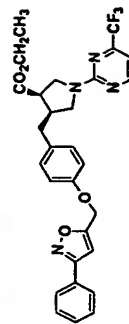
Example 257

5

[M + H]<sup>+</sup> = 525.3Example 258

10

A.



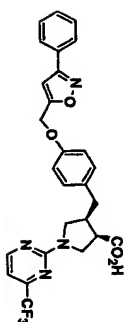
15

A mixture of 5-chloromethyl-3-phenylisoxazole (14.7 mg; 0.076 mmol), Example 243 Part A compound (15 mg; 0.038 mmol) and K<sub>2</sub>CO<sub>3</sub> (10.5 mg; 0.076 mmol) in CH<sub>3</sub>CN (1 mL) was heated at 90°C for 16 h, then was cooled to RT and partitioned between EtOAc (10 mL) and H<sub>2</sub>O (5 mL). The organic phase was washed with brine (20 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to provide crude Part A compound as an oil, which was used in the next step without further purification.

25

- 333 -

B.



A solution of crude Part A compound and LiOH·H<sub>2</sub>O

(8.0 mg; 0.19 mmol) in THF (1.2 mL) and H<sub>2</sub>O (0.6 mL) was stirred at 60 °C for 12 h, then was cooled to RT and the pH was adjusted to ~2 with aqueous 1 N HCl. The mixture was partitioned between EtOAc (10 mL) and H<sub>2</sub>O (5 mL).

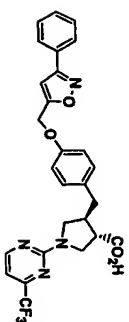
The organic phase was washed with brine (20 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was

purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30 : 70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give two compounds. The compound with the shorter retention time was lyophilized from 1,4-dioxane to give the title compound (4.0 mg; 20% for 2 steps) as a white solid.

[M + H]<sup>+</sup> = 525.3

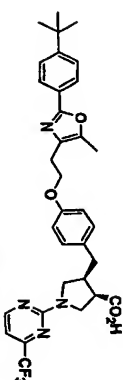
The second compound (longer retention time) was determined to be the corresponding epimerized trans-isomer of Example 258. This compound was also lyophilized from 1,4-dioxane to give Example 259 (1.0 mg; 5.0% for 2 steps) as a white solid.

#### Example 259

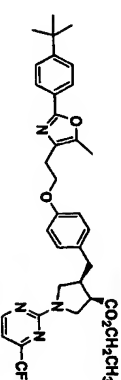


[M + H]<sup>+</sup> = 525.3

#### Example 260



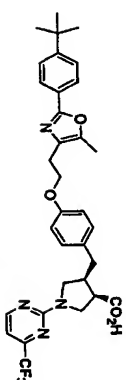
A.



To a solution of Example 243 Part A compound (16 mg; 0.0405 mmol) in toluene (0.4 mL) were successively added

Example 233 Part A compound (15.7 mg; 0.0608 mmol) and cyanomethylene tri-n-butylphosphorane (29.4 mg; 0.122 mmol). The reaction mixture was heated to 80°C for 8 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30 : 70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give Part A compound (7.3 mg; 28%).

B.



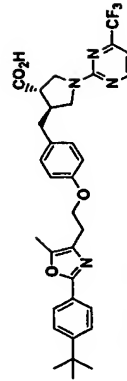
A solution of Part A compound (7.3 mg; 0.011 mmol) and LiOH·H<sub>2</sub>O (8.5 mg; 0.202 mmol) in THF (1.2 mL) and H<sub>2</sub>O (0.6 mL) was stirred at 60°C for 15 h, then was cooled to RT and the pH was adjusted to ~2 with aqueous 1 N HCl. The mixture was partitioned between EtOAc (10 mL) and H<sub>2</sub>O (5 mL). The organic phase was washed with brine (20 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was

purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30:70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give two compounds. The compound with the shorter retention time was lyophilized from 1,4-dioxane to give the title compound (2.6 mg; 39%) as a white solid.

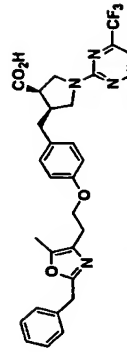
$$[M + H]^+ = 609.5$$

The second compound (longer retention time) was determined to be the corresponding epimerized trans-isomer of Example 260. This compound was also lyophilized from 1,4-dioxane to give Example 261 (1.2 mg; 4.9% for two steps) as a white solid.

### Example 261


$$(\text{M} + \text{H})^+ = 609.4$$

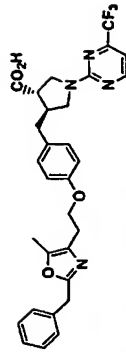
### Example 262



The title compound (4.8 mg; 21%) was prepared from Example 229 Part B compound (13.2 mg; 0.0608 mmol) and Example 243 Part A compound according to the procedure described for the synthesis of Example 261.

$[M + H]^+ = 567.4$

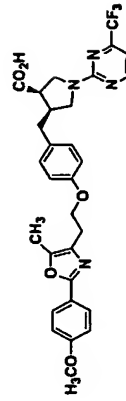
### Example 263



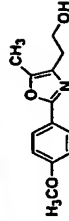
The title compound (1.2 mg; 5.2%) was obtained from Example 229 Part B compound (13.2 mg; 0.0608 mmol) and according to the general procedure described for the synthesis of Example 262.

$[M + H]^+ = 567.4$

### Example 264

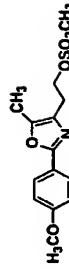


15 A.



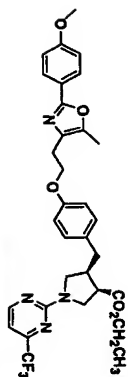
Part A compound was synthesized according to the general procedure described for the synthesis of Example 231 Part A compound except that 4-methoxybenzoyl chloride was used instead of 3-chlorobenzoyl chloride.

B.



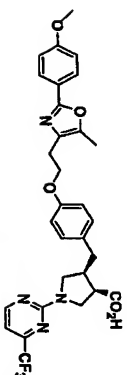
Part B compound was synthesized from Part A compound according to the general procedure described for the synthesis of Example 23 Part A compound.

2



A mixture of Example 243 Part A compound (20 mg; 0.051 mmol), Part B compound (24 mg; 0.076 mmol) and  $K_2CO_3$  (21 mg; 0.152 mmol) in  $CH_3CN$  (1.0 mL) was stirred at 90 °C for 22 h, then was cooled to RT and partitioned between EtOAc (10 mL) and  $H_2O$  (5 mL). The organic phase was washed with brine (20 mL), dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30:70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give Part C compound (14.5 mg; 47%).

D.

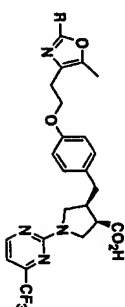


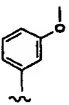

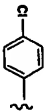
A solution of Part C compound (14.5 mg; 0.0238 mmol) in HOAc/concentrated HCl (1.2 mL of a 9:1 solution) was stirred at 75°C for 18 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30:70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give the title compound (7.3 mg; 53%) as a white solid.

$[M + H]^+ = 583.2$

Examples 265-267

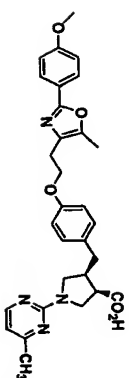
Examples 265-267 of the invention were prepared in a similar fashion to Example 264 using appropriately substituted phenyl oxazole mesylates.



Example #	R	[M + H] <sup>+</sup>
265		583.1
266		587.1
267		587.1

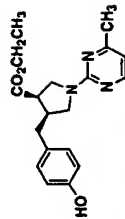
10

### Example 268



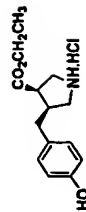
15

A.



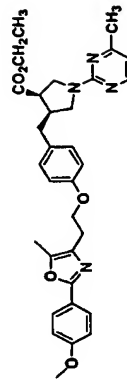
A mixture of Example 229 Part C compound (70 mg;

5 0.28 mmol)



10 and 2-chloro-4-methyl-pyrimidine (36 mg; 0.28 mmol) and  $i\text{Pr}_3\text{NET}$  (97.5  $\mu\text{L}$ ; 0.56 mmol) in toluene (2.3 mL) was stirred at 80°C for 2 h, then was cooled to RT and partitioned between EtOAc (15 mL) and aqueous 1 M HCl (10 mL). The organic phase was washed with  $\text{H}_2\text{O}$  (2 x 15 mL) and brine (20 mL), dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 90% hex to 100% EtOAc) to give Part A compound (82 mg; 86%) as a colorless oil.

B.

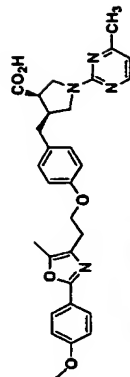


20

A mixture of Part A compound (15 mg; 0.044 mmol), Example 264 Part B compound (23.3 mg; 0.0748 mmol) and  $\text{K}_2\text{CO}_3$  (10.9 mg; 0.0792 mmol) in  $\text{CH}_3\text{CN}$  (1.0 mL) was stirred at 90°C for 30 h, then was cooled to RT and partitioned between EtOAc (10 mL) and  $\text{H}_2\text{O}$  (5 mL). The organic phase was washed with brine (20 mL), dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give crude Part B compound, which was used in the next step without further purification.

30

C.



5 A solution of crude Part B compound in HOAc/

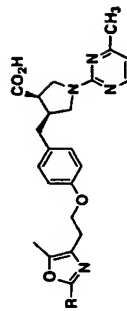
concentrated HCl (1.0 mL of a 9:1 solution) was stirred at 75 °C for 18 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30:70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give the title compound (3.8 mg; 16% for 2 steps) as a white solid.  $[\text{M} + \text{H}]^+ = 529.1$

15

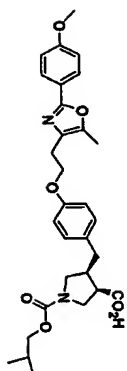
Example 269-270

Example 269-270 of the invention were prepared in the same ways as Example 268 using appropriate mesylates (synthesized as for Example 264 Part B compound).

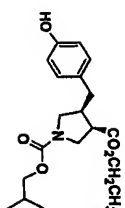
20



Example #	R	$[\text{M} + \text{H}]^+$
269		529.1
270		533.1

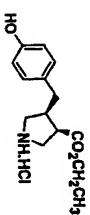
Example 271

5 A.



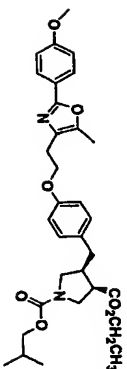
A mixture of Example 229 Part C compound (476 mg; 1.91 mmol),

10



isobutyl chloroformate (248  $\mu$ L; 1.91 mmol) and  $\text{NaHCO}_3$  (241 mg; 2.87 mmol) in dioxane:H<sub>2</sub>O (9.6 mL of a 2:1 solution) was stirred at RT for 3 h, then was partitioned between EtOAc (150 mL) and H<sub>2</sub>O (100 mL). The organic phase was washed with brine (140 mL), dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 90% hex to 100% EtOAc) to give Part A compound (513 mg; 77%) as a colorless oil.

B.

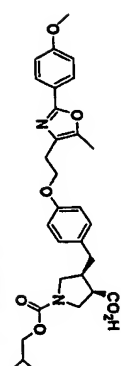


A mixture of Part A compound (20 mg; 0.057 mmol), Example 264 Part B compound (32 mg; 0.104 mmol) and  $\text{K}_2\text{CO}_3$  (14.2 mg; 0.104 mmol) in  $\text{CH}_3\text{CN}$  (1.0 mL) was stirred at

- 342 -

90°C for 30 h, then was cooled to RT and partitioned between EtOAc (10 mL) and H<sub>2</sub>O (5 mL). The organic phase was washed with brine (20 mL), dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give crude Part B compound, which was used in the next step without further purification.

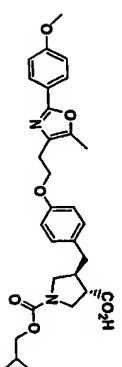
C.



A solution of crude Part B compound in HOAc/concentrated HCl (1.0 mL of a 9:1 solution) was stirred at 75°C for 18 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 30:70 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give two compounds. The compound with the shorter retention time was lyophilized from 1,4-dioxane to give the title compound (8.5 mg; 28%) as a white solid.

[M + H]<sup>+</sup> = 537.3

The second compound (longer retention time) was determined to be the corresponding epimerized trans-isomer of Example 271. This compound was also lyophilized from 1,4-dioxane to give Example 272 (5.8 mg; 19% for two steps) as a white solid.

Example 272

- 343 -



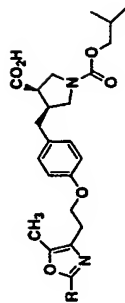
$[M + H]^+ = 537.2$

Example 273-274

5

Example 273 through 274 of the invention were prepared in a similar fashion to Example 272 using appropriately substituted phenyloxazole mesylates.

10



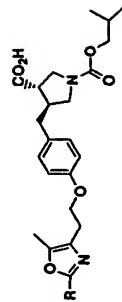
Example #	R	$[M + H]^+$
273		537.3
274		541.2

15

Example 275-276

Example 275-276 of the invention were obtained in a similar fashion to Example 272. They were determined to be the corresponding epimerized trans-isomers of Examples 273-274.

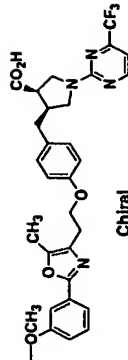
20



Example #	R	$[M + H]^+$
275		537.2
276		541.2

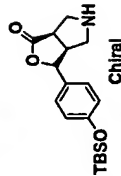
5

Example 277

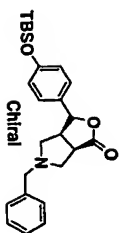


10

A.



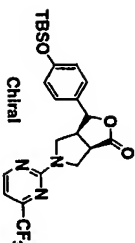
Example 184 Part D compound (200 mg; 0.46 mmol.)



was stripped from from toluene (2 x 10 mL), dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL), cooled to  $0^\circ\text{C}$  and  $\alpha$ -chloroethyl

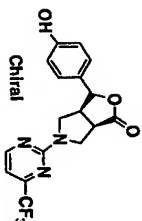
- 5 chloroformate (0.16 g, 1.2 mmol) was added. The solution was heated at  $56^\circ\text{C}$  for 2 h, then cooled to RT and concentrated in vacuo. The residue was stripped from toluene, dissolved in MeOH (5 mL) and stirred for 2 h and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; 9:1  $\text{CH}_2\text{Cl}_2$ :MeOH with 0.1% of  $\text{NH}_4\text{OH}$ ) give Part A
- 10 Compound as a clear oil (0.1 g; 66%)

B.



- 15 To a solution of Part A Compound (0.1, 0.3 mmol) in toluene (5 mL) was added 2-chloro-4-trifluoromethyl-pyrimidine (81 mg, 0.45 mmol) and  $\text{iPr}_2\text{NEt}$  (57 mg, 0.45 mmol). The solution was stirred for 5 h at  $80^\circ\text{C}$ , then cooled to RT and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; 4:1 EtOAc:hex) to give Part B
- 20 compound as a clear oil (89 mg; 80%).

C.

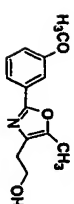


25

- A mixture of Part B compound (290 mg; 0.61 mmol) and tetrabutylammonium fluoride (1.22 mL of a 1 M solution in THF; 1.22 mmol) in THF (3.1 mL) was stirred at RT for 3 h, after which the reaction was partitioned between EtOAc (60 mL) and  $\text{H}_2\text{O}$  (30 mL). The organic phase was washed with brine (40 mL), dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 9:1 hex:EtOAc to 100% EtOAc) to give Part C
- 5 compound (140 mg; 63%) as a colorless oil.

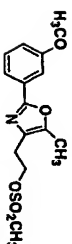
10

D.



- Part D compound was synthesized according to the general procedure described for the synthesis of Example 231 Part A compound except that 4-methoxybenzoyl chloride was used instead of 3-chlorobenzoyl chloride.

E.

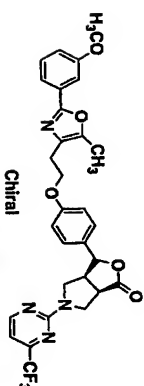


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Part E compound was synthesized from Part D compound according to the general procedure described for the synthesis of Example 23 Part A compound.

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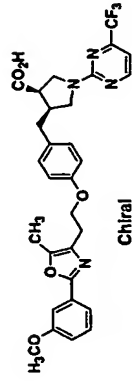
F.



- A mixture of Part C compound (47 mg; 0.129 mmol), Part E compound (60 mg; 0.193 mmol) and  $\text{K}_2\text{CO}_3$  (36 mg; 0.258 mmol) in  $\text{CH}_3\text{CN}$  (1.5 mL) was stirred at  $90^\circ\text{C}$  for 18

h, then was cooled to RT and partitioned between EtOAc (10 mL) and H<sub>2</sub>O (5 mL). The organic phase was washed with brine (20 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to give crude Part F compound, which was used in the next step without further purification.

G.

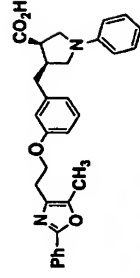


A mixture of crude Part F compound and 10% Pd/C (8 mg) in MeOH (1.5 mL) was stirred under an atmosphere of H<sub>2</sub> (balloon) at RT for 18 h. The catalyst was filtered off (Celite®) and the filtrate was concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 1 except that a continuous gradient from 40:60 Solvent A:Solvent B to 100% B over 10 min was used, followed by 4 min hold at 100% B) to give the title compound (3.0 mg; 4% for 2 steps) as a white solid.

[M + H]<sup>+</sup> = 583.1

20

#### Example 278



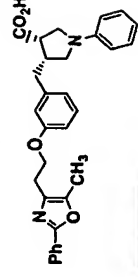
A mixture of Example 21 Part E compound (130 mg; 0.299 mmol), phenylboronic acid (50 mg; 0.41 mmol), Cu(OAc)<sub>2</sub> (5 mg; 0.027 mmol), 2,6 lutidine (0.5 mL) and molecular sieves (4 Å) in toluene (2 mL) was stirred at RT for 24 h in air. At this point HPLC showed that product had been formed. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. A solution of the residue in acetic acid/concentrated HCl

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(2 mL of a 3:1 solution) was stirred at 70°C for 18 h. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (as described for Example 1) to provide the title compound (28 mg; 19.4%) as an oil.

[M + H]<sup>+</sup> = 483.1, [α]<sub>D</sub><sup>25</sup> = -18.3° (c = 1.0; 25°C)  
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.03-8.01 (2H, dd, J = 1.8 Hz), 7.56-7.48 (3H, m), 7.37-7.33 (2H, t, J = 7.4 Hz), 7.26-7.24 (2H, m), 7.17-7.13 (2H, m), 6.71-6.75 (3H, m), 4.27-4.18 (2H, m), 4.11-4.06 (1H, m), 3.79-3.76 (1H, dd, J = 4.4 Hz), 3.62-3.58 (1H, m), 3.47-3.42 (1H, t, J = 10 Hz), 3.38-3.33 (1H, m), 3.14-3.07 (3H, m), 2.97-2.92 (1H, dd, J = 6.1 Hz), 2.67-2.61 (1H, dd, J = 4.8 Hz), 2.46 (3H, s)

#### Example 279



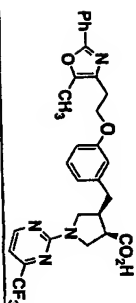
15

The titled compound (41 mg; 28.4%) was prepared from Example 21 Part E compound (using the same sequence as the synthesis of Example previous compound).

[M + H]<sup>+</sup> = 483.1 [α]<sub>D</sub><sup>25</sup> = 20°, (c=1.0; 25°C)  
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.03-8.00 (2H, dd, J = 1.8 Hz), 7.56-7.48 (3H, m), 7.37-7.33 (2H, t, J = 7.4 Hz), 7.26-7.24 (2H, m), 7.17-7.13 (2H, m), 6.71-6.75 (3H, m), 4.27-4.18 (2H, m), 4.11-4.06 (1H, m), 3.79-3.76 (1H, dd, J = 4.4 Hz), 3.62-3.58 (1H, m), 3.47-3.42 (1H, t, J = 10 Hz), 3.38-3.34 (1H, m), 3.14-3.04 (3H, m), 2.98-2.93 (1H, dd, J = 6.1 Hz), 2.62-2.56 (1H, dd, J = 4.8 Hz), 2.44 (3H, s)

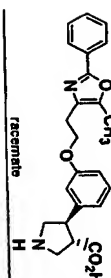
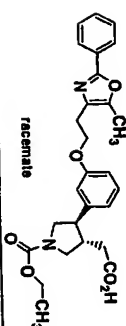
30

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Example 280

5 A mixture of Example 21 Part E compound (50 mg; 0.115 mmol), 2-Chloro-4-(trifluoromethyl)-pyrimidine (21 mg; 0.115 mmol), Et<sub>3</sub>N (50 mg; 0.5 mmol) in toluene (3 mL) was stirred at 50°C for 1 h in air. The reaction mixture was concentrated in vacuo. A solution of the residue in acetic acid/concentrated HCl (2 mL of a 3:1 solution) and stirred at 80°C for 18 h. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (as described for Example 1) to provide the title compound (60 mg; 90%) as a white solid.

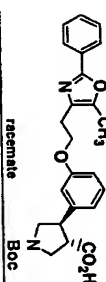
15 [M + H]<sup>+</sup> = 553.3, [α]<sub>D</sub><sup>25</sup> = -37.7°; (c=1.25; 25°C)  
<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.55 (1H, s), 8.01-7.99 (2H, d, J = 8 Hz), 7.53-7.46 (3H, m), 7.12-7.21 (1H, m), 6.84-6.69 (4H, m), 4.17-4.27 (2H, t, J = 8 Hz), 3.98-4.08 (1H, m), 3.50-3.80 (3H, m), 3.18-3.30 (1H, m), 3.03-3.13 (2H, t, J = 8 Hz), 2.77-2.96 (2H, m), 2.57-2.67 (1H, m), 2.44 (3H, s)

Example 281

25 A.

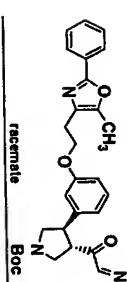
5 A mixture of Example 12 Part C compound (550 mg; 0.92 mmol) and 10% Pd/C (30 mg) in MeOH (10 mL) under an atmosphere of H<sub>2</sub> was stirred at RT for 2 h. At this point analytical HPLC showed that the reaction was complete. The catalyst was filtered off (using a pad of Celite®) and the filtrate was concentrated in vacuo to give crude Part A compound as an oil which was used in the next reaction without further purification.

10 B.



15 A mixture of crude Part A compound and di-tert butyl dicarbonate (300 mg; 1.3 mmol) in saturated aqueous NaHCO<sub>3</sub> (5 mL) and THF (5 mL) was stirred at RT for 2 h, then was partitioned between EtOAc and H<sub>2</sub>O (20 mL each). The organic phase was concentrated in vacuo and the residue was purified by preparative HPLC (as described for Example 1) to give the title compound (237 mg; 52% for 2 steps) as an oil.

20 C.



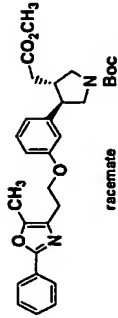
25 Step 1. Preparation of diazomethane:

To a solution of aqueous KOH (40% 2 mL) and diethyl ether (5 mL) was added 1-Methyl-3-nitro-1-nitrosoguanidine (176 mg; 1.2 mmol) slowly at 0°C and the reaction was stirred at 0°C for a further 30 min. The aqueous phase was removed and the top yellow organic phase containing diazomethane was dried with solid KOH (1 g) at 0°C and was used for the next step without further purification.

## Step 2. Preparation of diazoketone:

To a solution of Part B compound (237 mg; 0.48 mmol) in THF (10 mL) and N-methylmorpholine (61 mg; 0.6 mmol) was cooled to -20°C and added isobutyl chloroformate (82 mg; 0.6 mmol) over 5 min. The reaction was stirred at -20°C for a further 30 min and then was added to the solution of CH<sub>2</sub>N<sub>2</sub> (from Step 1) at 0°C. After stirring at 0°C for 30 min, the reaction was stirred at RT for another 3 h, then was concentrated in vacuo; the residue was chromatographed (SiO<sub>2</sub>; 3:1 Hex:EtOAc) to give Part C compound (150 mg; 60%) as an oil.

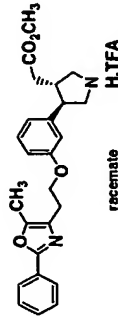
D.



15

To a solution of Part C compound (150 mg; 0.29 mmol) in anhydrous MeOH (1 mL) was added a solution of silver benzoate (15 mg; 0.065 mmol) in Et<sub>3</sub>N (0.7 mL) and the reaction was stirred at RT for 30 min, after which EtOAc (10 mL) was added. The solution was washed with 1N aqueous HCl (5 mL) and H<sub>2</sub>O (5 mL x 2), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 3:1 Hex:EtOAc) to give Part D compound (78 mg; 31%) as an oil.

E.

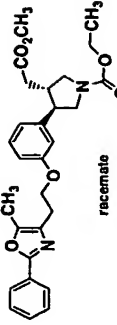


25

A solution of Part D compound (78 mg; 0.15 mmol) and TFA (1 mL) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at RT for 30 min. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (as described for example 1) to give Part E compound (80 mg; 99%).

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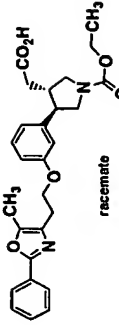
F.



To a 0°C solution of Part E compound (10 mg; 0.018 mmol) and DMAP (12 mg; 0.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added dropwise ethyl chloroformate (4 µL; 0.032 mmol). The reaction mixture was allowed to warm to RT and stirred at RT for 3 h. At this point HPLC indicated that all starting material had been consumed. The solid was filtered through SiO<sub>2</sub> with Hex:EtOAc (3:1) and the filtrate was concentrated in vacuo to give the Crude (SiO<sub>2</sub>; Hex:EtOAc 3:1) to provide crude Part F compound as an oil.

15

G.



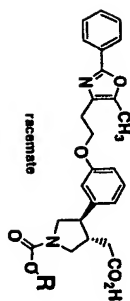
A solution of Part F compound in aqueous LiOH (1 mL of a 1 M solution) and THF (1 mL) was stirred at RT for 2 h; TLC indicated that the reaction was complete at this point. The reaction mixture was acidified with aqueous HCl (2 mL of a 1 M solution) and extracted with EtOAc (2 x 2 mL). The organic phase was washed with H<sub>2</sub>O (2 x 2 mL) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1) to provide the title compound (7.4 mg; 85.9%) as an oil. [M + H]<sup>+</sup> = 479.2

30

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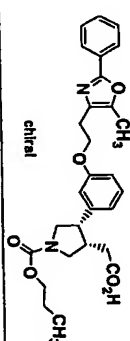
Examples 282-288

Examples 282 through 288 were prepared in a similar fashion to the previous Example using the appropriate chloroformates.

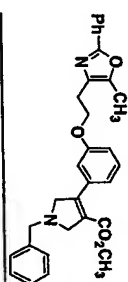


Example #	R	[M + H] <sup>+</sup>
282		491.3
283		493.3
284		507.3
285		527.2
286		545.2
287		557.2

Example #	R	[M + H] <sup>+</sup>
288		541.2

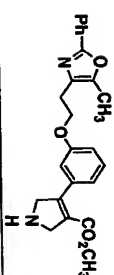
Example 289

A.



A mixture of Example 36 Part B compound (2 g; 2.77 mmol), Example 1 Part B compound (0.8 g; 3.0 mmol) and TFA (1 drop) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was stirred at RT for 3 h, then was concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; hex:EtOAc 1:1) to give Part C compound (1.66 g; 64%) as an oil.

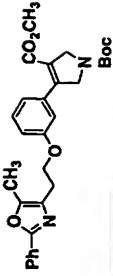
B.



To a -78°C solution of Part A compound (2.5 g; 5.05 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added CH<sub>3</sub>CHClCOCl (0.5 mL; 4.45 mmol). The reaction mixture was stirred at -78°C for 30 min, then was allowed to warm to RT and stirred at RT

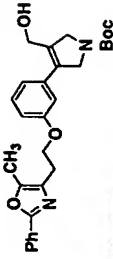
for 1 h. At this point, HPLC indicated that all starting material had been consumed. Volatiles were removed in vacuo and MeOH (10 mL) was added; the solution was then stirred at RT for 8 h. Volatiles were removed in vacuo to give crude Part B compound, which was used in the next step without further purification.

C.



10 A solution of crude Part B compound and di-tert butyl dicarbonate (800 mg; 3.66 mmol) in saturated aqueous NaHCO<sub>3</sub> (10 mL) and THF (10 mL) was stirred at RT for 2 h, then was partitioned between EtOAc and H<sub>2</sub>O (20 mL). The organic phase was concentrated in vacuo and the residue was chromatographed (SiO<sub>2</sub>; Hex:EtOAc 3:1) to give Part C compound (2.1 g; 82% for two steps) as an oil.

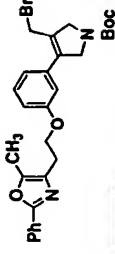
D.



20 To a -70°C solution of Part C compound (373 mg; 0.74 mmol) in anhydrous THF (3 mL) was added DIBALH (1.5 mL of a 1 M solution in hexane; 1.5 mmol) dropwise. The reaction was stirred at -70°C for 20 min, then was warmed to RT and stirred at RT for 2 h, then re-cooled to -70°C and quenched by dropwise addition of MeOH (1 mL). The mixture was allowed to warm to RT, aqueous Rochelle salt (10 mL of a 1 M solution) was added and stirring was continued for 1 h. The mixture was partitioned between H<sub>2</sub>O and Et<sub>2</sub>O (20 mL each). The aqueous phase was extracted with additional Et<sub>2</sub>O (20 mL); the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in

vacuo to give crude Part D compound, which was used in the next step without further purification.

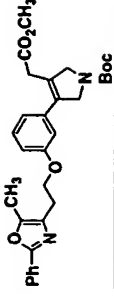
E.



5

To a 0°C solution of crude Part C compound and Ph<sub>3</sub>P (232 mg; 0.89 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added CBr<sub>4</sub> (294 mg; 0.89 mmol) portionwise. The reaction was allowed to warm to RT and stirred at RT for 2 h, then was concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; hex:EtOAc 3:1) to give Part E compound (270 mg; 68% for two steps) as an oil.

F.

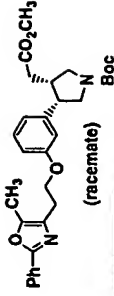


15

A mixture of Part E compound (270 mg; 0.5 mmol), (Ph<sub>3</sub>P)<sub>4</sub>Pd<sup>0</sup> (58 mg; 0.05 mmol) and K<sub>2</sub>CO<sub>3</sub> (200 mg; 2.0 mmol) in anhydrous MeOH (5 mL) in an autoclave was pressurized to 100 psi with carbon monoxide (vessel flushed 3X with CO). The reaction mixture was stirred at RT for 3 h, after which the CO gas was released and the mixture was filtered. The filtrate was concentrated in vacuo and the residue was chromatographed (SiO<sub>2</sub>; 3:1 hex:EtOAc) to give Part F compound (150 mg; 56%) as an oil.

25

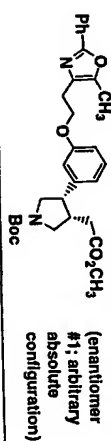
G.



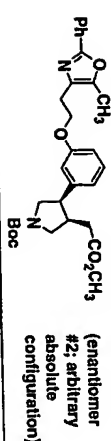
A suspension of Part F compound (150 mg; 0.29 mmol) and 10% Pd/C (10 mg) in MeOH (5 mL) was stirred at RT under an atmosphere of H<sub>2</sub> (balloon) for 2 h. The

catalyst was filtered off (Celite®) and the filtrate was concentrated in vacuo to give the Part G compound (147 mg; 56% for 2 steps) as an oil.

5 H.



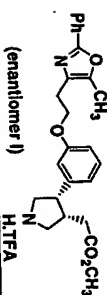
I.



10 The two enantiomers of racemic Part G compound

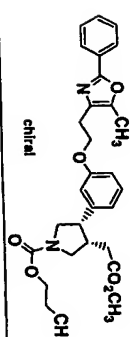
(147 mg; 0.283 mmol) were separated by preparative HPLC using the following conditions: ChiralPAK®AS 5 cm x 50 cm chiral column; flow rate = 40 mL/min; isocratic conditions = 93:7 isopropanol:hexane. Chiral analytical HPLC (Daicel Chiralcel AS 4.6 x 250 mm column): flow rate = 1.5 mL/min; isocratic conditions = 80:20 hexane:iPrOH; detector wavelength = 220 nm. Part G compound (Enantiomer I) was obtained (60 mg; 81.6%; retention time = 4.64 min; ee >95%) as an oil. Part H compound (Enantiomer II) was obtained (55 mg; 74.8%; retention time = 6.29 min; ee >90%) as an oil.

J.



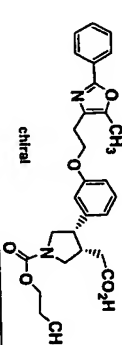
25 A solution of Part H compound (enantiomer I; 60 mg; 0.115 mmol) in TFA (0.5 mL) and CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) was stirred at RT for 2.5 h, then was concentrated in vacuo to give crude Part J compound as an oil, which was used in the next step without further purification.

K.



5 A mixture of crude Part J compound (0.038 mmol), DMAP (30 mg; 0.3 mmol) and n-propyl chloroformate (36 mg; 0.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at RT for 1 h, then was loaded onto a SiO<sub>2</sub> cartridge and flushed with EtOAc/Hexane (1:3) to give crude Part K compound.

10 L.



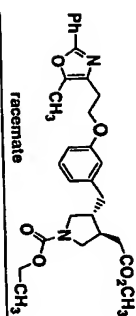
15 A solution of Part K compound in aqueous LiOH (1 mL of a 1 M solution) and THF (1 mL) was stirred at RT for 2 h; TLC indicated that the reaction was complete at this point. The reaction mixture was acidified with aqueous HCl (2 mL of a 1 M solution) and extracted with EtOAc (2 mL). The organic phase was washed with H<sub>2</sub>O (2 x 2 mL) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1) to provide the title compound (28 mg; 95%) as an oil. [M + H]<sup>+</sup> = 493.2, [α]<sub>D</sub><sup>25</sup> = 25.5; (c = 0.65; 25°C) <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.02-8.0 (2H, dd, J = 8 Hz), 7.6-7.46 (3H, m), 7.23-7.19 (1H, t, J = 12 Hz), 6.78-6.65 (3H, m), 4.3-4.07 (4H, m), 3.85-3.52 (4H, m), 3.20-3.1 (1H, m), 3.09-3.01 (2H, t, J = 6.2 Hz), 2.98-2.89 (1H, m), 2.44 (3H, s), 2.20-2.11 (1H, m), 1.96-1.85 (1H, m), 1.74-1.62 (2H, m), 0.97-0.95 (3H, m)

30



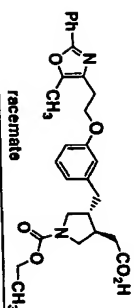


C.



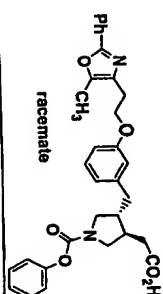
To a solution of Part B compound (180 mg; 0.36 mmol) in anhydrous MeOH (4 mL) was added a solution of PhCO<sub>2</sub>Ag (146 mg; 0.7 mmol) in Et<sub>3</sub>N (5 mL) and the reaction was stirred at RT for 30 min, after which the reaction was partitioned between EtOAc (5 mL) and 1N aqueous HCl (5 mL x 1). The organic phase was washed with H<sub>2</sub>O (5 mL x 2), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give crude Part C compound.

D.



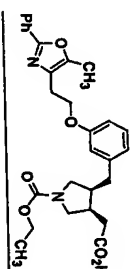
A solution of crude Part D compound in aqueous LiOH.H<sub>2</sub>O (1 mL of a 1 M solution) and THF (2 mL) was stirred at RT for 3 h; TLC indicated that the reaction was complete at this point. The reaction mixture was acidified with aqueous HCl (2 mL of a 1 M solution) and extracted with EtOAc (2 mL). The organic phase was washed with H<sub>2</sub>O (2 x 2 mL) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1) to provide the title compound (160 mg; 90% for two steps) as an oil.

[M + H]<sup>+</sup> = 493.2  
<sup>1</sup>HNMR (CDCl<sub>3</sub>): δ 8.03-8.0 (2H, m), 7.56-7.51 (3H, m), 7.19-7.15 (1H, m), 6.76-6.70 (3H, m), 4.24-4.21 (2H, m), 4.12-4.07 (2H, q, J = 7.0 Hz), 3.83-3.74 (1H, m), 3.53-3.41 (1H, m), 3.13-3.01 (4H, m), 2.83-2.77 (1H, m), 2.55-2.43 (2H, m), 2.40 (3H, s), 2.34-2.13 (3H, m), 1.27-1.19 (3H, m)

Example 294

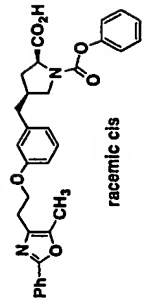
The title compound (16 mg; 32%) was prepared from Example 3 compound (using the same sequence as for the synthesis of Example 293 except that phenyl chloroformate was used instead of ethyl chloroformate).

[M + H]<sup>+</sup> = 541.3  
<sup>1</sup>HNMR (CDCl<sub>3</sub>): δ 8.03-8.00 (2H, m), 7.56-7.49 (3H, m), 7.33-7.28 (2H, m), 7.19-7.15 (2H, m), 7.08-7.05 (2H, m), 6.75-6.71 (3H, m), 4.25-4.23 (2H, t, J = 5 Hz), 3.98-3.85 (1H, m), 3.70-3.58 (1H, m), 3.31-3.13 (2H, m), 3.11-3.09 (2H, t, J = 5 Hz), 2.86-2.80 (1H, m), 2.61-2.57 (2H, m), 2.48 (3H, s), 2.34-2.13 (3H, m)

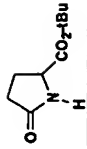
Example 295

The title (15 mg; 42% yield overall for 3 steps) was prepared from Example 22 compound by the same sequence as for the synthesis of Example 293.  
 [M + H]<sup>+</sup> = 493.2; [α]<sub>D</sub><sup>25</sup> = -16.1° (c=0.6; 25°C)  
<sup>1</sup>HNMR (CDCl<sub>3</sub>): δ 8.03-8.02 (2H, m), 7.56-7.51 (3H, m), 7.19-7.15 (1H, m), 6.76-6.70 (3H, m), 4.25-4.22 (2H, t, J = 5.72 Hz), 4.13-4.08 (2H, m), 3.57-3.53 (1H, m), 3.33-3.09 (6H, m), 2.75-2.07 (8H, m), 1.25-1.22 (3H, m)

## Example 296



A.

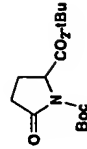


5

A solution of DL-pyrogutamic acid (5 g; 0.039 mol, HClO<sub>4</sub> (1.25 mL of a 70% solution) in tert-butyl acetate (60 mL) was stirred at RT for 18h, then was poured into saturated aqueous NaHCO<sub>3</sub> (100 mL) and ice. The mixture was extracted with EtOAc (20 mL x 3). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give Part A compound as white crystals (4.36 g; 60.3%).

15

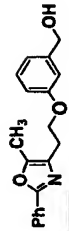
B.



A mixture of Part A compound (4.36 g; 23.5 mmol); di-tert-butyl dicarbonate (10.7 g; 50 mmol) and DMAP (6.1 g; 50 mmol) in MeCN (20 mL) was stirred at RT for 18 h. Volatiles were removed in vacuo and the residue was chromatographed (SiO<sub>2</sub>; Hex:EtOAc 1:1) to give part B compound (6.6 g; 98.4%) as an oil.

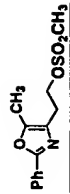
25

C.



A mixture of 3-hydroxybenzyl alcohol (2 gm; 16 mmol), the mesylate Example 23 Part A compound (2.0 g; 7.11 mmol)

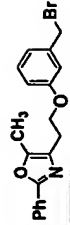
- 364 -



and K<sub>2</sub>CO<sub>3</sub> (5.0 g; 36 mmol) in MeCN (100 mL) was stirred at 80°C for 10 h. At this point LC/MS showed that the reaction was complete. The reaction was cooled to RT, solids were filtered off, and the filtrate was partitioned between EtOAc (100 mL) and aqueous 1 M HCl (10 mL). The organic phase was successively washed with 1 M NaOH (10 mL) and H<sub>2</sub>O (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 2:1 Hex:EtOAc) to give Part C compound (2.15 g; 98%) as white crystals.

15

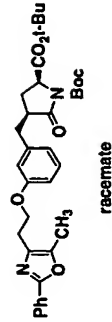
D.



A mixture of Part C compound (2.15 g; 6.95 mmol), PBr<sub>3</sub> (10 mL of a 1 M solution in CH<sub>2</sub>Cl<sub>2</sub>) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was stirred at RT for 0.5 h. Volatiles were removed in vacuo. The residue was chromatographed (SiO<sub>2</sub>; Hex:EtOAc 3:1) to give part D compound (2.0 g; 75%) as white crystals.

25

E.

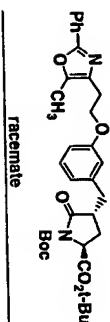


To a -74°C solution of Part B compound (200 mg; 0.7 mmol) in THF (5 mL) was added LiN(TMS)<sub>2</sub> (1.2 mL of a 1 M solution in THF) dropwise. The reaction was stirred at -74°C for 40 min, after which a solution of Part D compound (200 mg; 0.54 mmol) in THF (5 mL) was added dropwise at -60°C. The reaction mixture was stirred at

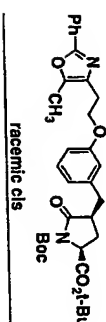
- 365 -

-60°C for 2 h, then was quenched by dropwise addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (1 mL). The mixture was allowed to warm to RT, then extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), concentrated in vacuo and the crude residue was chromatographed ( $\text{SiO}_2$ ; Hex:EtOAc 3:1) to give both the desired *cis* isomer (27 mg; 6.5%) Part E compound as well as the *trans* isomer Part F compound (8.7 mg; 2.4%) as oils.

## Part F compound:



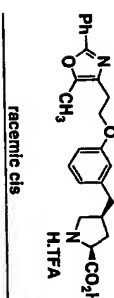
## Part G compound:



To a -74°C solution of Part E compound (*cis* isomer; 27 mg; 0.047 mmol) in THF (5 mL) under  $\text{N}_2$  was added  $\text{LiEt}_3\text{BH}$  (0.06 mL of a 1 M solution in THF). The reaction was stirred at -74°C for 30 min, then was quenched by dropwise addition of saturated aqueous  $\text{NaHCO}_3$  (1 mL) and one drop of  $\text{H}_2\text{O}_2$ . The mixture was allowed to warm to RT, then extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. To a -74°C solution of the crude product and  $\text{Et}_3\text{SiH}$  (7.5  $\mu\text{L}$ ; 1M solution in THF; 0.06 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added  $\text{BF}_3\cdot\text{OEt}_2$  (7.6  $\mu\text{L}$ ; 0.06 mmol). The reaction was stirred at -74°C for 30 min, after which more  $\text{Et}_3\text{SiH}$  (7.5  $\mu\text{L}$ ) and  $\text{BF}_3\cdot\text{OEt}_2$  (7.6  $\mu\text{L}$ ) was added. The reaction was warmed to RT and stirred at RT for another 30 min, after which it was quenched by

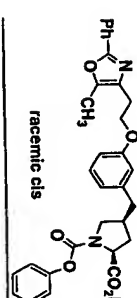
dropwise addition of saturated aqueous  $\text{NaHCO}_3$  (1 mL), then extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 10 mL). The combined organic extracts were dried with  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; Hex:EtOAc 2:1) to provide Part G compound (23 mg, 80%).

## H.



A solution of Part H compound and TFA (1 mL) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was stirred at RT for 1 h, after which volatiles were removed in vacuo to give crude Part H compound (15 mg; 79%), which was used in the next step without further purification.

## I.



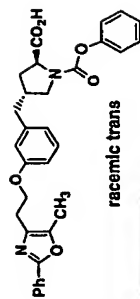
A solution of crude Part I compound, saturated aqueous  $\text{NaHCO}_3$  (2 mL) and phenyl chloroformate (50  $\mu\text{L}$ ; 0.36 mmol) in THF (2 mL) was stirred at RT for 30 min, then was partitioned between EtOAc and  $\text{H}_2\text{O}$  (10 mL each). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was purified by preparative HPLC (as described for Example 1) to provide the title compound (19 mg; 76.7%) as an oil.

$[\text{M} + \text{H}]^+ = 527.3$

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.98-7.94 (2H, m), 7.49-7.10 (9H, m), 6.75-6.68 (3H, m), 4.54-4.20 (3H, m), 3.88-3.74 (1H, m), 3.57-3.42 (1H, m), 3.02-2.99 (2H, t, J = 5 Hz), 2.83-2.74

(2H, m), 2.58-2.50 (1H, m), 2.40-2.33 (4H, m), 2.02-1.92 (1H, m)

### Example 297

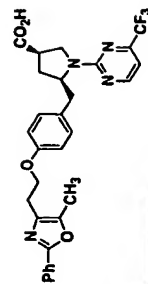


This trans isomer (6.6 mg; 83.5%) was prepared from Part F compound (using the same sequence as for the synthesis of previous Cis isomer).

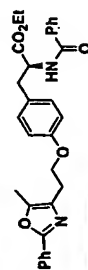
[M + H]<sup>+</sup> = 527.3

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.03-7.98 (2H, m), 7.56-7.47 (3H, m), 7.35-7.27 (2H, m), 7.22-7.05 (4H, m), 6.75-6.69 (3H, m), 4.61-4.49 (1H, m), 4.23-4.20 (2H, t, J = 8.0 Hz), 3.79-3.70 (1H, m), 3.29-3.20 (1H, m), 3.09-3.06 (2H, t, J = 8 Hz), 2.78-2.60 (3H, m), 2.45 (3H, s), 2.40-1.92 (2H, m)

### Example 298



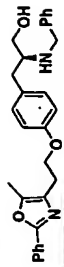
A.



A mixture of N-benzoyl-L-tyrosine ethyl ester (1.0 g; 3.19 mmol), 5-phenyl-2-methyl-oxazole-4-ethanol (650 mg; 3.19 mmol) and cyanomethylene-tri-n-butylphosphorane (1.15 g; 4.79 mmol) in toluene (10 mL) was stirred at 70°C for 3 h, then was concentrated in vacuo. The

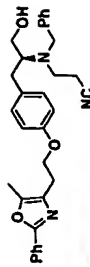
residue was chromatographed (SiO<sub>2</sub>; Hex:EtAc 2:1) to provide Part A compound (1.28 g; 81%) as yellowish crystals.

5 B.



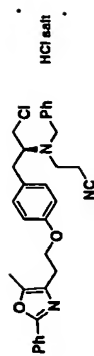
A solution of Part A compound (500 mg; 1.0 mmol), LiAlH<sub>4</sub> (2 mL of a 1 M solution in THF) in THF was stirred at 50°C for 1 h, then MeOH (1 mL) was added slowly, follow by aqueous Rochelle salt (5 mL of a 1 M solution). The mixture was stirred at RT for 18 h and filtered. The filtrate was diluted with Et<sub>2</sub>O (20 mL) and washed with H<sub>2</sub>O (3 x 30 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part B compound (394 mg; 89%) as white solid.

C.



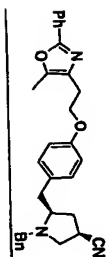
A solution of Part B compound (300 mg; 0.68 mmol), acrylonitrile (4.3 mL) and HOAc (41 μL) in EtOH (5 mL) was stirred at 75°C for 30 h, then was cooled to RT and partitioned between EtOAc (20 mL) and aqueous NaOH (10 mL of a 1 M solution). The organic phase was washed with H<sub>2</sub>O (2 x 30 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The crude residue was chromatographed (SiO<sub>2</sub>; 2:1 Hex:EtOAc) to give Part C compound (180 mg; 89%) as an oil.

30 D.



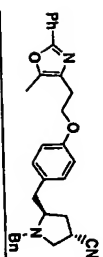
A mixture of Part C compound (182 mg; 0.367 mmol) and  $\text{SOCl}_2$  (0.25 mL; 3.4 mmol) in  $\text{CHCl}_3$  (5 mL) was heated at reflux for 30 min, then was cooled to RT. 100 mL  $\text{Et}_2\text{O}$  was added and the mixture was filtered; the recovered solids were dried in vacuo to give Part D compound (200 mg; 99%) as white solid.

E.

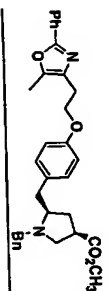


To a RT solution of Part D compound (200 mg; 0.36 mmol) in THF (5 mL) under  $\text{N}_2$  was added dropwise  $\text{NaN}(\text{TMS})_2$  in THF (0.80 mL of a 1 M solution; 0.80 mmol). The reaction was stirred at RT for 1 h, then was quenched by addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (1 mL). The mixture was extracted with  $\text{EtOAc}$  (10 mL). The organic phase was washed with water (2 x 10 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The crude residue was chromatographed ( $\text{SiO}_2$ ; 2:1 Hex: $\text{EtOAc}$ ) to give Part E compound (21 mg; 24%) as an oil in addition to the trans isomer Part F compound (21 mg; 24%).

Part F compound:



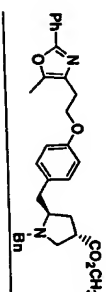
G.



A mixture of Part E compound (21 mg; 0.044 mmol) in  $\text{H}_2\text{SO}_4\text{:MeOH}$  (10%; 2 mL) was stirred at  $80^\circ\text{C}$  for 72 h, then was cooled to RT, the mixture was partitioned

between  $\text{EtOAc}$  and  $\text{H}_2\text{O}$  (10 mL each). The organic phase was washed with  $\text{H}_2\text{O}$  (2 x 10 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The crude residue was chromatographed ( $\text{SiO}_2$ ; 1:1 Hex: $\text{EtOAc}$ ) to give Part G compound (20 mg; 89%) as an oil.

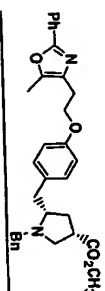
H.



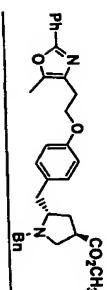
Part H compound (20 mg; 89%) was prepared from Part F compound (using the same procedure as the preparation of Part G compound from Part E compound) as an oil.

Part I compound (18 mg; 80%) and Part J compound (19 mg; 82%) were both prepared from N-benzoyl-D-tyrosine ethyl ester (using exactly the same sequence as the synthesis of Part G compound and Part H compound).

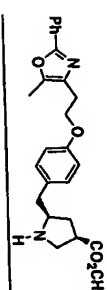
Part I compound:



Part J compound:

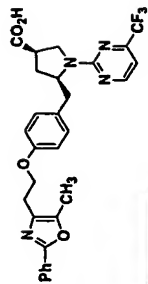


K.



A solution of Part G compound (20 mg; 0.039 mmol) and  $\text{CH}_3\text{CHClOCOCl}$  (5  $\mu\text{L}$ ; 0.05 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was stirred at RT for 18 h. Volatiles were removed in vacuo and MeOH (2 mL) was added; the solution was then stirred at RT for 8 h. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (YMC reverse-phase ODS 30 x 250 mm column; flow rate = 25 mL/min; 30 min continuous gradient from 30:70 B:A to 100% B + 10 min hold-time at 100% B, where solvent A = 90:10:0.1  $\text{H}_2\text{O}:\text{MeOH}:\text{TFA}$  and solvent B = 90:10:0.1  $\text{MeOH}:\text{H}_2\text{O}:\text{TFA}$ ) to provide Part K compound (16 mg; 80%) as a TFA salt.

L.



15

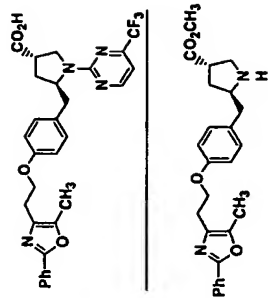
A mixture of Part K compound (16 mg; 0.038 mmol), 2-Chloro-4-(trifluoromethyl)-pyrimidine (10 mg; 0.04 mmol) and  $\text{Et}_3\text{N}$  (25 mg; 0.25 mmol) in toluene (2 mL) was stirred at 60°C for 2 h, then was cooled to RT and concentrated in vacuo. A solution of the residue in HOAc/concentrated HCl (5 mL of a 3:1 solution) was stirred at 75°C for 18 h. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (as described for Example 1) to provide the title compound (5.4 mg; 30%) as a white solid.

$[\text{M} + \text{H}]^+ = 553.2$

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.50-8.49 (1H, d, J = 4 Hz), 7.91-7.90 (2H, m), 7.40-7.30 (3H, m), 7.09-7.07 (2H, d, J = 8 Hz), 6.78-6.73 (3H, m), 4.28 (1H, s, broad), 4.15-4.13 (2H, t, J = 4 Hz), 4.00 (1H, s, br), 3.85 (1H, s, br), 3.28-3.26 (1H, d, J = 8 Hz), 3.07-3.05 (1H, m), 2.98-2.92 (2H, t, J = 4 Hz), 2.45 (1H, s, br), 2.32 (3H, s), 2.24-2.16 (2H, m)

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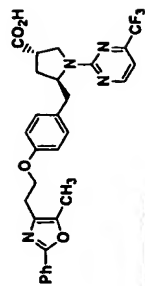
Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 100:7 A:B, where A = heptane + 0.1% TFA; B IPA + 0.1% TFA; detector wavelength = 220 nm; retention time = 23 min; ee > 90%

Example 299

10 A.

Part A compound was prepared from Example 298 Part H compound in exactly the same way as Example 298 Part K compound was prepared from Example 298 Part G compound.

B.



20 The title compound (6.9 mg; 42% overall for 3

steps) was prepared from Part A compound in exactly the same way as Example 298 compound was prepared from Example 298 Part K compound.

$[\text{M} + \text{H}]^+ = 553.3$

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.61-8.60 (1H, d, J = 4 Hz), 8.03-8.01 (2H, d, J = 8 Hz), 7.60-7.50 (3H, m), 7.12-7.10 (2H, d, J = 8 Hz), 6.88-6.87 (1H, m), 6.82-6.81 (2H, d, J = 8 Hz) 4.50 (1H, s, broad), 4.15-4.13 (2H, t, J = 4.8 Hz), 3.82-

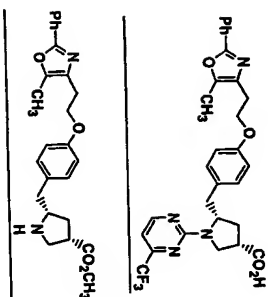
- 373 -

3.81 (2H, d,  $J = 7.0$  Hz), 3.13-3.10 (4H, m), 2.61 (1H, s, broad), 2.48 (3H, s), 2.18-2.16 (2H, m)  
 Chiral analytical HPLC (Daicel Chiralcel OD 4.6 x 500 mm column): flow rate = 1 mL/min; isocratic conditions = 93:7 A:B, where A = heptane + 0.1% TFA; B IPA + 0.1% TFA; detector wavelength = 220 nm; retention time = 32 min; ee > 90%

Example 300

10

A.

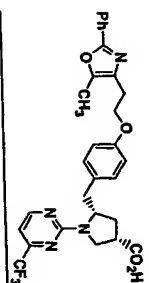


15

Part A compound was prepared from Example 298 Part I compound according to the method used to prepare Example 298 Part K compound from Example 298 Part G compound.

20

B.



The title compound (11.7 mg; 66% overall for 3 steps) was prepared from Part A compound (using the same sequence as for the synthesis of Example 299 compound).

[M + H]<sup>+</sup> = 553.3  
<sup>1</sup>HNMR (CDCl<sub>3</sub>):  $\delta$  8.57-8.56 (1H, d,  $J = 4$  Hz), 7.99-7.97 (2H, m), 7.44-7.38 (3H, m), 7.16-7.15 (2H, d,  $J = 8$  Hz), 6.83-6.82 (3H, m), 4.35 (1H, s, broad), 4.23-4.20 (2H,

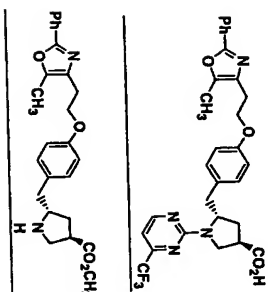
t,  $J = 8$  Hz), 4.07 (1H, s, broad), 3.94 (1H, s, broad), 3.36-3.33 (1H, d,  $J = 8$  Hz), 3.18-3.11 (1H, m), 3.02-3.00 (2H, m), 2.50 (1H, s, broad), 2.39 (3H, s), 2.30-2.20 (2H, m)

5 Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 90:10 A:B, where A = heptane + 0.1% TFA; B IPA + 0.1% TFA; detector wavelength = 220 nm; retention time = 13.45 min; ee > 90%

10

Example 301

A.

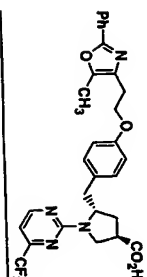


15

Part A compound was prepared from Example 298 Part J compound according to the method used to prepare Example 298 Part K compound from Example 298 Part G compound.

20

B.



The title compound (4.4 mg; 50% overall for 3 steps) was prepared from Part A compound (using the same sequence as for the synthesis of Example 299).

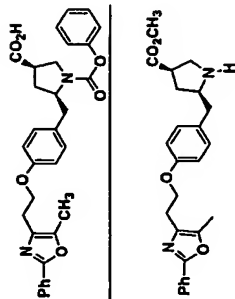
[M + H]<sup>+</sup> = 553.3



<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.61-8.60 (1H, d, J = 4 Hz), 8.03-8.01 (2H, d, J = 8 Hz), 7.58-7.50 (3H, m), 7.12-7.10 (2H, d, J = 8 Hz), 6.88-6.87 (1H, m), 6.83-6.81 (2H, d, J = 8 Hz), 4.50 (1H, s, broad), 4.23-4.21 (2H, t, J = 4.8 Hz), 3.82-3.81 (2H, d, J = 7.0 Hz), 3.13-3.10 (4H, m), 2.61 (1H, s, broad), 2.47 (3H, s), 2.18-2.16 (2H, m)

Chiral analytical HPLC (Daicel Chiralcel OD 4.6 x 500 mm column): flow rate = 1 mL/min; isocratic conditions = 93:7 A:B, where A = heptane + 0.1% TFA; B IPA + 0.1% TFA; detector wavelength = 220 nm; retention time = 39 min; ee > 90%

#### Example 302

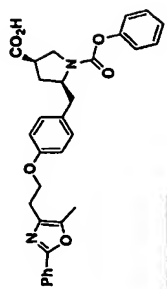


A.

A suspension of Example 298 Part G compound (34 mg; 0.066 mmol) and Pd-Black (20 mg) in HCO<sub>2</sub>H-MeOH (3 mL of a 9:1 solution) was stirred at RT for 1 h. The catalyst was filtered off and the filtrate was partitioned between EtOAc (5 mL) and aqueous NaOH (2 mL of a 1 M solution). The organic phase was washed with water, dried, (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give Part A compound (27 mg; 97.2%) as an oil which was used in the next step without further purification.

30

B.



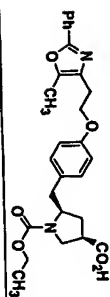
A mixture of Part A compound (18 mg; 0.042 mmol), DMAP (12 mg; 0.1 mmol) and phenyl chloroformate (15 μL; 0.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at RT for 2 h, then was partitioned between aqueous 1 N HCl and EtOAc. The organic phase was washed with H<sub>2</sub>O and brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. A mixture of the residual crude carbamate-ester in HOAc/concentrated HCl (5 mL of a 4:1 solution) was stirred at 80°C for 18 h, then was cooled to RT and concentrated in vacuo. The mixture was partitioned between EtOAc and H<sub>2</sub>O (5 mL each). The organic phase was concentrated in vacuo and the residue was purified by preparative HPLC (as described for Example 1) to give the title compound (11.6 mg; 71%) as a white solid.

[M + H]<sup>+</sup> = 527.1

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.99-7.97 (2H, m), 7.47-7.43 (3H, m), 7.40-7.3 (2H, m), 7.25-7.10 (5H, m), 6.82-6.80 (2H, d, J = 8 Hz), 4.50-4.10 (3H, m), 4.05-3.90 (1H, m), 3.75-3.63 (1H, m), 3.29-3.19 (1H, m), 3.18-3.01 (3H, m), 2.74-2.50 (1H, m), 2.40 (3H, s), 2.26-2.10 (2H, m)

Chiral analytical HPLC (Daicel Chiralcel OD 10 μm 4.6 x 250 mm column): flow rate = 1.0 mL/min; isocratic conditions = 85:15 A:B, where A = hexane with 0.1% TFA; B = isopropanol with 0.1% TFA; detector wavelength = 220 nm; retention time = 12.39 min; ee > 90%

30

Example 303

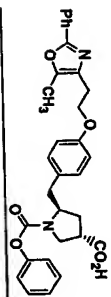
The title compound (12 mg; 78%) was prepared from Example 302 Part A compound (using the same sequence as for the synthesis of Example 302 except that ethyl chloroformate was used instead of phenyl chloroformate).

[M + H]<sup>+</sup> = 479.2

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.99-7.97 (2H, d, J = 8 Hz), 7.52-7.45 (3H, m), 7.06 (2H, s), 6.80-6.78 (2H, d, J = 8 Hz), 4.21-4.14 (4H, m), 4.01-3.79 (2H, m), 3.52-3.47 (1H, t, J = 8 Hz), 3.32-2.85 (4H, m), 2.56-2.47 (1H, m), 2.42 (3H, s), 2.23-1.89 (2H, m), 1.30-1.27 (3H, t, J = 8 Hz)

15 Chiral analytical HPLC (Daicel Chiralcel AD 10 um 4.6 x 250 mm column): flow rate = 1.0 mL/min; isocratic conditions = 90:10 A:B, where A = hexane with 0.1% TFA; B = isopropanol with 0.1% TFA; detector wavelength = 220 nm; retention time = 20.43 min; ee > 90%

20 Example 304



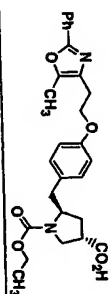
25 The title compound (15.6 mg; 70%) was prepared from Example 299 Part A compound using the same sequence as for the synthesis of Example 302 from Example 302 Part A compound.

[M + H]<sup>+</sup> = 527.1

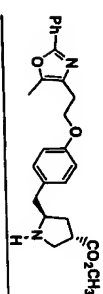
30 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.98-7.97 (2H, d, J = 8 Hz), 7.45-7.29 (5H, m), 7.23-7.02 (5H, m), 6.85-6.82 (2H, d, J = 8 Hz), 4.45-4.20 (3H, m), 3.82-3.56 (2H, m), 3.08-2.85 (4H, m), 2.62-2.80 (1H, m), 2.37 (3H, s), 2.13-2.03 (2H, m)

- 378 -

Chiral analytical HPLC (Daicel Chiralcel OD 10 um 4.6 x 250 mm column): flow rate = 1.0 mL/min; isocratic conditions = 85:15 A:B, where A = hexane with 0.1% TFA; B = isopropanol with 0.1% TFA; detector wavelength = 220 nm; retention time = 18.18 min; ee > 90%

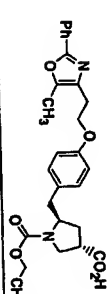
Example 305

10 A.



15 Part A compound (37 mg; 90%) was prepared from Example 298 Part H compound by the same procedure as the synthesis of Example 302 Part A compound from Example 298 Part G compound.

B.



20 The title compound (16 mg; 79%) was prepared according to the same procedure as the synthesis of Example 303 from Example 302 Part A compound.

[M + H]<sup>+</sup> = 479.2

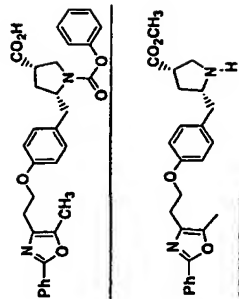
25 <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.00-7.97 (2H, m), 7.50-7.45 (3H, m), 7.05 (2H, s), 6.81-6.79 (2H, d, J = 8 Hz), 4.21-4.11 (5H, m), 3.65-3.48 (2H, m), 3.06-2.51 (5H, m), 2.42 (3H, s), 2.08-1.95 (2H, m), 1.29-1.26 (3H, t, J = 4 Hz)

30 Chiral analytical HPLC (Daicel Chiralcel AD 10 um 4.6 x 250 mm column): flow rate = 1.0 mL/min; isocratic conditions = 90:10 A:B, where A = hex with 0.1% TFA; B =

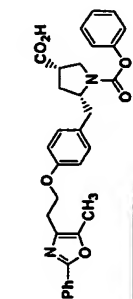
- 379 -

IPA with 0.1% TFA; detector wavelength = 220 nm;  
retention time = 27.23 min; ee > 90%

### Example 306



Part A compound (39 mg; 97%) was prepared from Example 298 Part I compound by the same procedure as Example Part A compound.

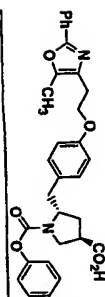


The title compound was prepared (12 mg; 47%) as prepared from Part A compound using the same procedure as for the synthesis of Example 302 from Example 302 Part A compound.

$$[M + H]^+ = 527.1$$

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.99-7.97 (2H, m), 7.52-7.43 (3H, m), 7.40-7.30 (2H, m), 7.23-7.00 (5H, m), 6.87-6.72 (2H, d, J = 8 Hz), 4.50-4.10 (3H, m), 4.05-3.90 (1H, m), 3.75-3.63 (1H, m), 3.29-3.19 (1H, m), 3.18-3.01 (3H, m), 2.74-2.50 (1H, m), 2.40 (3H, s), 2.26-2.10 (2H, m)

B.



The title compound (26 mg; 86%) was prepared from Part A compound using the same procedure as the synthesis of Example 302 from Example 302 Part A compound.

$[M + H]^+ = 527.1$

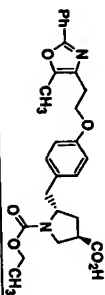
$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.98-7.97 (2H, d,  $J = 8$  Hz), 7.45-7.29 (5H, m), 7.23-7.02 (5H, m), 6.85-6.82 (2H, d,  $J = 8$  Hz), 4.45-4.20 (3H, m), 3.84-3.54 (2H, m), 3.13-2.85 (4H, m), 2.62-2.80 (1H, m), 2.37 (3H, s), 2.13-2.03 (2H, m)

Chiral analytical HPLC (Daicel Chiralcel OD 10  $\mu\text{m}$  4.6 x 250 mm column): flow rate = 1.0 mL/min; isocratic

conditions = 85:15 A:B, where A = HEX with 0.1% TFA; B = IPA with 0.1% TFA; detector wavelength = 220 nm;

15 retention time = 21 min; ee > 90%

#### Example 309



20 The title compound (18.4 mg; 67%) was prepared from Example 308 Part A compound as for Example 302, except

that ethyl chloroformate was used instead of phenyl chloroformate.

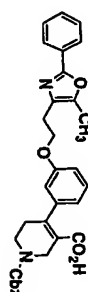
25  $[M + H]^+ = 479.2$

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.00-7.97 (2H, m), 7.50-7.45 (3H, m), 7.05 (2H, s), 6.81-6.79 (2H, d,  $J = 8$  Hz), 4.21-4.11 (5H, m), 3.65-3.48 (2H, m), 3.06-2.86 (4H, m), 2.51-2.69 (1H, m), 2.42 (3H, s), 2.08-1.95 (2H, m), 1.29-1.26 (3H, t,  $J = 4$  Hz)

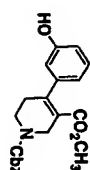
Chiral analytical HPLC (Daicel Chiralcel AD 10  $\mu\text{m}$  4.6 x 250 mm column): flow rate = 1.0 mL/min; isocratic

conditions = 90:10 A:B, where A = HEX with 0.1% TFA; B = IPA with 0.1% TFA; detector wavelength = 220 nm; retention time = 29.50 min; ee > 90%

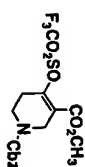
#### Example 310



A.



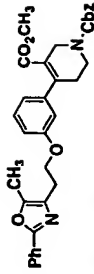
A mixture of tetrahydropyridine-3-carbomethoxy triflate (0.58 g; 1.3 mmol)



(prepared according to the procedure of Astles, P. C., et. al., PCT Int. Appl (2001), WO 0190101), 3-hydroxy-phenylboronic acid (0.24 g; 1.7 mmol),  $(\text{Ph}_3\text{P})_4\text{Pd}^0$  (0.41 g; 0.35 mmol), and tetrabutylammonium bromide (0.57 g; 1.7 mmol) in dioxane (10 mL) was stirred for 5 h at 90°C, then was cooled to RT and concentrated in vacuo. The residue was partitioned between EtOAc and brine. The organic layer was dried ( $\text{MgSO}_4$ ) and concentrated concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 9:1 hexane:EtOAc) to give Part A Compound (0.35 g; 70%).

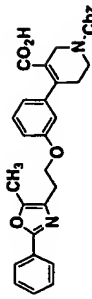
30

B.



A mixture of Part A Compound (0.2 g 0.57 mmol),  
 5 Example 23 Part A compound (0.19 g; 0.69 mmol) and  $K_2CO_3$  (0.095 g; 0.69 mmol) in MeCN (10 mL) was stirred for 8 h at 80°C, then cooled to RT and concentrated in vacuo. The residue partitioned between EtOAc and brine. The organic layer was dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; 4:1 hex:EtOAc) to give Part B Compound (0.15 g; 50%) as an oil.

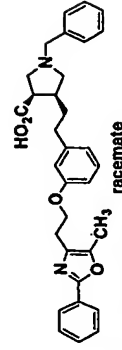
C.



A solution of Part B Compound (0.1 g; 0.28 mmol) and aqueous KOH (2 mL of a 1 N solution) in MeOH (5 mL) was stirred at RT for 18 h, then was concentrated in vacuo.  
 20 The residue was neutralized with aqueous 1 N HCl and extracted with EtOAc (3x). The combined organic extracts were dried ( $Na_2SO_4$ ) and concentrate in vacuo to give the title compound.  
 [M + H]<sup>+</sup> = 553.2

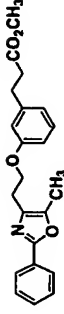
25

### Example 311

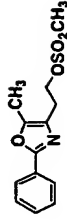


30

A.



A mixture of 3-(3-hydroxyphenyl)-propionic acid  
 5 methyl ester (3.12 g; 17.3 mmol), Example 23 Part A compound (4.86 g; 17.3 mmol)

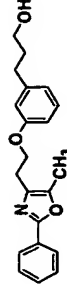


10 and  $K_2CO_3$  (4.9 g; 36 mmol) in MeCN (100 mL) was heated overnight at 90°C in an oil bath. Volatiles were removed in vacuo, and the residue was partitioned between  $H_2O$  and EtOAc. The aqueous phase was extracted with EtOAc (2x) and the combined organic extracts were dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; continuous gradient from 100% hex to 100% EtOAc) to give a mixture of the product and unreacted phenol, which was washed repeatedly with aqueous 2N NaOH to furnish purified Part A compound (4.0 g; 63%) as a pale yellow solid.

[M + H]<sup>+</sup> = 366.3

20

B.



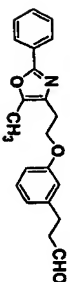
25

To a 0°C solution of Part A compound (2.02 g; 5.55 mmol) in anhydrous THF (30 mL) was cautiously added portionwise solid  $LiAlH_4$  (290 mg; 7.63 mmol). The reaction was allowed to warm to RT and stirred at RT overnight, then was cautiously quenched with excess aqueous 1 N HCl (30 mL). The mixture was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried ( $Na_2SO_4$ ) and concentrated in vacuo to

30

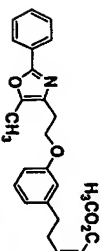
give Part B compound (1.90 g; 100% crude), which was used in the next reaction without further purification.  
[M + H]<sup>+</sup> = 324.4

# C.



To a RT suspension of Dess-Martin periodinane (3.6 g; 8.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added dropwise a solution of Part B compound (1.90 g; 5.64 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) over 5 min. The reaction was stirred at RT for 4.5 h, then was concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to give Part C compound (1.70 g; 90%) as a colorless oil.

# E.



Reference: Sano, S.; Yokoyama, K.; Fukushima, M.; Yagi, T.; Nagao, Y. *Chem. Commun.* **1997**, 6, 559-560

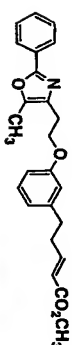
To a -78°C suspension of NaH (65 mg of a 60% mixture; 1.63 mmol) in anhydrous THF (10 mL) under N<sub>2</sub> was added (CF<sub>3</sub>CH<sub>2</sub>O)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub> (380 μL; 1.79 mmol) dropwise. The solution was stirred at -78°C for 10 min, after which a solution of Part C compound (343 mg; 1.02 mmol) in THF (5 mL) was added dropwise over 5 min. The reaction mixture was stirred for 6 h at -78°C (a significant amount of Part C compound remained at this point), then was allowed to warm slowly to RT and stirred overnight at RT. Excess saturated aqueous NH<sub>4</sub>Cl was added and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuo, and the residue was

chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to give the Z-isomer Part D compound (199 mg; 50%) as a colorless oil as well as the E-isomer Part E compound (86 mg; 22%) as a colorless oil.

# Part D compound (Z-isomer) data:

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.27 (s, 3H), 2.62 (t, J = 7.7 Hz, 2H), 2.83-2.90 (m, 4H), 3.58 (s, 3H), 4.14 (t, J = 6.6 Hz, 2H), 5.69 (dt, J = 11.4, 1.8 Hz, 1H), 6.12 (dt, J = 11.4, 7.5 Hz, 1H), 6.6-6.72 (m, 3H), 7.08 (t, J = 7.9, 1H), 7.28-7.35 (m, 3H), 7.89 (dd, J = 7.9, 1.8 Hz, 2H).

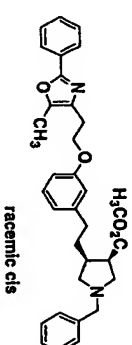
# E.



# Part E compound (E-isomer) data:

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.29 (s, 3H), 2.38-2.46 (m, 2H), 2.64 (t, J = 7.9 Hz, 2H), 2.90 (t, J = 6.6 Hz, 2H), 3.63 (s, 3H), 4.16 (t, J = 6.8 Hz, 2H), 5.75 (dt, J = 15.8, 1.8 Hz, 1H), 6.6-6.7 (m, 3H), 6.90 (dt, J = 15.4, 7.0 Hz, 1H), 7.1 (t, J = 7.9, 1H), 7.3-7.4 (m, 3H), 7.90 (dd, J = 7.9, 1.8 Hz, 2H).

# F.



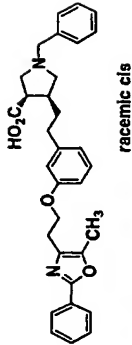
# 25

To a solution of Part D compound (126 mg; 0.32 mmol) in toluene (4 mL) were successively added Example 1 Part B compound (192 mg; 1.23 mmol) and TFA (4 drops).

The reaction was stirred at RT for 2 h, after which more Example 1 Part B compound (100 mg) was added. Volatiles were removed in vacuo and the residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to

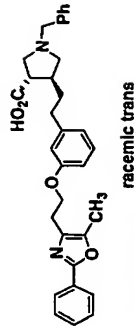
provide Part F compound (189 mg; contains some unreacted Example 1 Part B compound; 100%) as a colorless oil.

G.



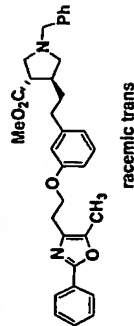
5

A mixture of Part F compound (24 mg; 0.046 mmol) in 20% aqueous HCl (0.25 mL) and HOAc (0.75 mL) was stirred at 80°C for 3 h, after which volatiles were removed in vacuo. The residue was purified by preparative HPLC (YMC ODS 20 x 100 mm reverse phase column, 10 min. continuous gradient from 50:50 A:B to 100% B according to the procedure in Example 1), then lyophilized from dioxane to provide the title compound (7 mg; 25%) as a white solid.

[M + H]<sup>+</sup> = 511.6Example 312

20

A.



To a solution of Example 311 Part E compound (70 mg, 0.179 mmol) in toluene (3 mL) was added Example 1 Part B compound (0.4 g, 1.68 mmol) followed by TFA (2 drops). The mixture was stirred for 16 h at RT, evaporated in

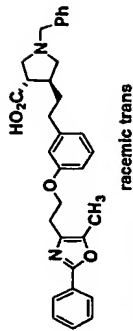
25

vacuo and the residue was chromatographed (SiO<sub>2</sub>; 100% hex to 100% EtOAc) to afford Part A compound (34 mg, 36%) as a colorless oil.

[M + H]<sup>+</sup> = 525.5

5

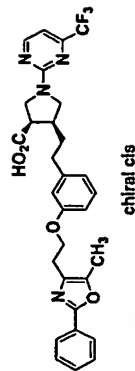
B.



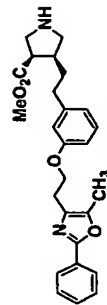
A solution of Part A compound (34 mg, 0.065 mmol) in 20% HCl:HOAc (1 mL of a 1:3 solution) was heated at 80°C for 3 h, then cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (YMC ODS 20 x 100 mm reverse phase column, 10 min continuous gradient from 70:30 A:B to 100% B, according to the conditions described for the purification of Example 1) and lyophilized from dioxane to afford the title compound (12.8 mg, 32%) as a white solid.

[M + H]<sup>+</sup> = 511.6

20

Example 313

A.

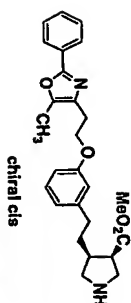


25

A mixture of Example 311 Part F compound (5.1 g, 9.7 mmol) in 30% HCOOH-MeOH (50 mL) and Pd black (1 g)

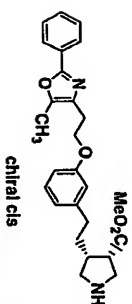
was stirred at RT for 16 h. The catalyst was filtered off; the filtrate was evaporated in vacuo and the residue was partitioned between EtOAc and saturated aqueous  $\text{NaHCO}_3$ . The aqueous layer was extracted with EtOAc (x 2) and the combined organic layers were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated in vacuo to yield Part A compound (4.3 g; 9.9 mmol; 100%) as a colorless oil.

## B.

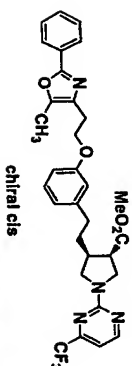


Part A compound (racemate) was separated into the two individual enantiomers by preparative HPLC (Chiralpak AD chiral column, 5 cm x 50 cm, 20  $\mu$ ; isocratic 20% EtOH-MeOH (1:1) + 85% heptane, flow rate = 45 mL/min) to afford Part B compound (1.8 g; faster-eluting enantiomer) and Part C compound (2.0 g; slower-eluting enantiomer) as colorless oils. The absolute stereochemistry of the two enantiomers is arbitrarily assigned.

## C.



## D.

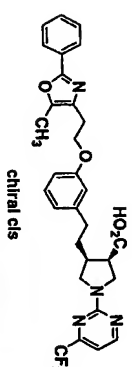


A mixture of Part B compound (20 mg, 0.046 mmol), 2-chloro-4-trifluoromethylpyrimidine (24 mg, 0.131 mmol) and  $i\text{-Pr}_3\text{NEt}$  (26  $\mu\text{L}$ , 0.15 mmol) in 0.5 mL toluene was stirred at RT for 1 h, then was concentrated in vacuo.

The residue was purified by preparative HPLC (YMC ODS 20 x 100 mm reverse phase column, 10 min continuous gradient from 20:80 A:B to 100% B according to the procedure in Example 1) to yield Part D compound (22 mg; 82%) as a colorless oil. The absolute stereochemistry of Part D compound is arbitrarily assigned.

$[M + H]^+ = 581.4$

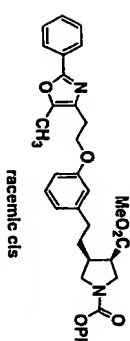
## E.



A solution of Part D compound (22 mg, 0.038 mmol) in 20% HCl:HOAc (1:3; 1 mL) was heated at 70°C for 19 h, then was concentrated in vacuo. The residue was purified by preparative HPLC (Phenomenex Luna 5 $\mu$  C18(2) 21.2 x 100 mm reverse phase column, 10 min. continuous gradient from 20:80 A:B to 100% B as described in the general procedure in Example 1) to afford the title compound (13.5 mg, 63%) as a colorless oil.

$[M + H]^+ = 567.4$

## Example 314



The title compound (racemate) was prepared according to the sequence described for the synthesis of Example 318

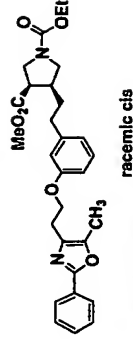


using phenyl chloroformate and Example 313 Part A compound (racemate).

$[M + H]^+ = 541.5$

5

Example 315



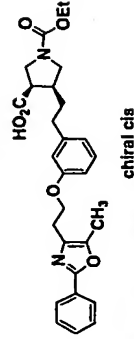
The title compound (racemate) was prepared using ethyl chloroformate and Example 313 Part A compound (racemic) according to the sequence described for the synthesis of Example 318.

$[M + H]^+ = 493.5$

10

15

Example 316

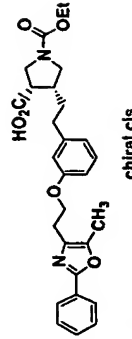


The title compound was prepared in the same way as for Example 315, but using Example 313 Part B compound (chiral).

$[M + H]^+ = 493.3$

25

Example 317

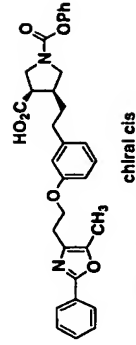


The title compound was synthesized in the same way as Example 316, but from Example 313 Part C compound and ethyl chloroformate.

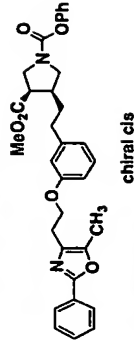
$[M + H]^+ = 493.3$

5

Example 318

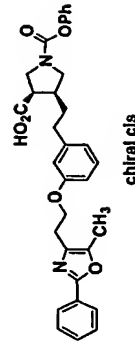


10 A.



To a solution of Example 313 Part B compound (120 mg, 0.286 mmol) in  $CH_2Cl_2$  (5 mL) was added  $Et_3N$  (80  $\mu L$ , 0.575 mmol) followed by phenyl chloroformate (50  $\mu L$ , 0.4 mmol) at RT. The reaction mixture was stirred for 3 h at RT, then was partitioned between  $CH_2Cl_2$  (25 mL) and 1N aqueous HCl (20 mL). The organic phase was washed with brine, dried ( $Na_2SO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ , continuous gradient from 100% hex to 100% EtOAc) to afford Part A compound (144 mg, 91%) as a colorless oil.

B.



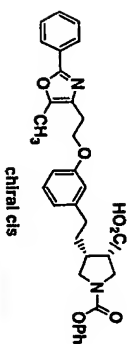
25

A solution of Part A compound (144 mg, 0.26 mmol) in 20% HCl:HOAc (3 mL of a 1:3 solution) was heated at

70°C for 19 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (YMC ODS 20 x 100 mm reverse phase column, 10 min continuous gradient from 20:80 A:B to 100%B according to the general procedure for Example 1) afforded the title compound (135 mg, 96%) as a pale yellow solid. The absolute stereochemistry is arbitrarily assigned.

[M + H]<sup>+</sup> = 541.38

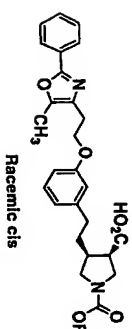
### Example 319






The title compound was prepared in the same manner as for the synthesis of Example 318 using Example 313 Part C compound and phenyl chloroformate. The absolute stereochemistry is arbitrarily assigned.

### Examples 320-330

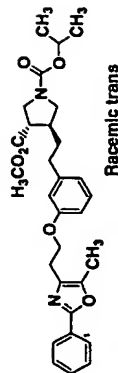
Examples 320-330 of the invention were prepared as part of a library using the same sequence for the preparation of Example 318 starting from racemic cis Example 313 Part A compound and an appropriate chloroformate.



Example Number	R	[M + H] <sup>+</sup>
320		507.6
321		507.6
322		521.6
323		521.6
324		535.6
325		555.6
326		559.6
327		575.5

Example Number	R	[M + H] <sup>+</sup>
328		619.5
329		555.6
330		571.6

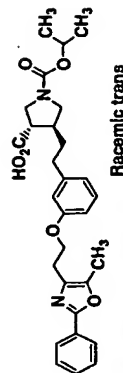
B.



Crude Part A compound (24 mg, 0.05 mmol) was

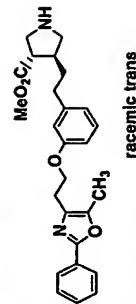
5 reacted with isopropyl chloroformate (60  $\mu$ L; 0.06 mmol), Et<sub>3</sub>N (40  $\mu$ L, 0.287 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) as in Example 318 Part A compound to give Part B compound as an oil which was used in the next step without further purification.

10 C.



Part B compound was hydrolyzed to the acid using the same procedure as for Example 318 Part B to give the 15 title compound (3.6 mg; 14% for 3 steps) as a colorless solid.

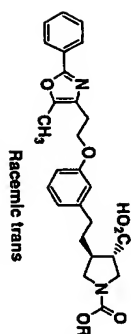
A.



10 A mixture of Example 312 Part A compound (240 mg, 0.46 mmol) and Pd black (235 mg) in 30% HCOOH-MeOH (5 mL) was stirred at RT for 3.5 h. The catalyst was filtered off; the filtrate was concentrated in vacuo and partitioned between EtOAc and saturated aqueous NaHCO<sub>3</sub>. 15 The aqueous layer was extracted with EtOAc (x 2) and the combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated in vacuo to yield crude Part A compound (220 mg; 100%, purity ~ 92%) as a colorless oil.

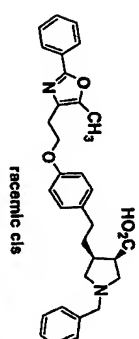
Examples 332-339

Examples 332-339 of the invention were prepared as part of a library in using the same sequence as for the synthesis of Example 331 (from Example 331 Part A 25 compound and appropriate chloroformates).

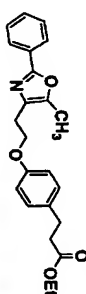


Example Number	R	[M + H] <sup>+</sup>
332		521.7
333		521.6
334		535.7
335		559.6
336		575.6
337		619.6
338		555.6
339		571.6

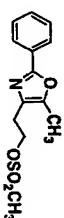
## Example 340



5 A.

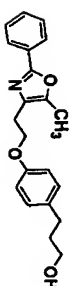


A mixture of 4-hydroxyphenylpropanoic acid ethyl ester (1.8 g; 9.28 mmol), Example 23 Part A compound (2.63 g; 9.36 mmol)



and K<sub>2</sub>CO<sub>3</sub> (2.65 g; 19.2 mmol) in MeCN (50 mL) was heated overnight at 90°C in an oil bath. Volatiles were removed in vacuo and the residue was partitioned between H<sub>2</sub>O and EtOAc. The aqueous phase was extracted with EtOAc (2x) and the combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to give part A compound (1.9 g, 54%) as a white solid. [M + H]<sup>+</sup> = 380.3

B.

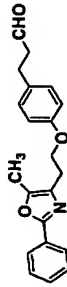


25

To a 0°C solution of Part A compound (1.87 g; 5 mmol) in anhydrous THF (30 mL) was cautiously added portionwise solid LiAlH<sub>4</sub> (295 mg; 7.6 mmol). The reaction

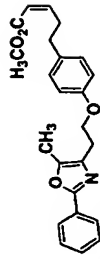
mixture was allowed to warm to RT, stirred at RT overnight, then was cautiously quenched with excess aqueous 1 N HCl. The mixture was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to give crude Part B compound (1.49 g; 88%) as a golden oil.

10 C.



To a RT suspension of Dess-Martin periodinane (2.1 g; 4.95 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was added dropwise a solution of Part B compound (1.49 g; 4.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) over 5 min. The reaction was stirred at RT for 1 h, then was concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to give Part C compound (1.41 g; 95%) as a colorless solid.

D.



To a -78°C suspension of NaH (340 mg of a 60% mixture; 8.5 mmol) in anhydrous THF (40 mL) under N<sub>2</sub> was added (CF<sub>3</sub>CH<sub>2</sub>O)P(O)(CH<sub>3</sub>)CO<sub>2</sub>CH<sub>3</sub> (2.2 mL; 10.41 mmol) dropwise. The solution was stirred at -78°C for 10 min, after which a solution of Part C compound (1.41 g; 4.21 mmol) in THF (10 mL) was added dropwise over 5 min. The reaction mixture was then allowed to warm slowly to RT and stirred overnight at RT. Excess saturated aqueous NH<sub>4</sub>Cl was added and the mixture was extracted with EtOAc (3x). The combined organic extracts were washed with

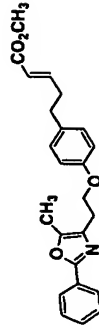
brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuo, and the residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to give the Z-isomer Part D compound (1.16 g; 70.2%) as a colorless oil as well as the E-isomer Part E compound (209 mg; 12.7%) as a colorless solid.

LC-MS for Part D: [M + H]<sup>+</sup> = 392.3;

TLC: R<sub>f</sub> (7:3 hex: EtOAc) = 0.43 (Part D compound, Z-isomer).

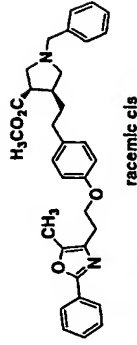
10

E.



15 TLC: R<sub>f</sub> (7:3 hex: EtOAc) = 0.36 (Part E compound, E-isomer)

F.



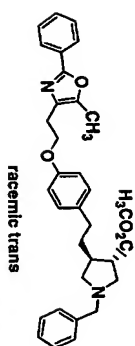
racemic cis

20

To a solution of Part D compound (1.04 g, 2.66 mmol) in toluene (10 mL) was added Example 1 Part B compound (1.0 gm, 4.2 mmol) followed by TFA (5 drops). The mixture was stirred for 16 h at RT, concentrated in vacuo and the residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to afford Part F compound (1.26 g, 91%) as a colorless oil. [M + H]<sup>+</sup> = 525.4

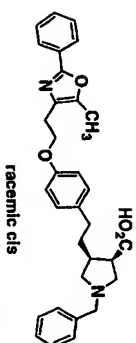
30

G.



Part G compound (trans isomer) was prepared (in a similar manner to Part F compound) from Part E compound (E-alkene) in quantitative yield.

H



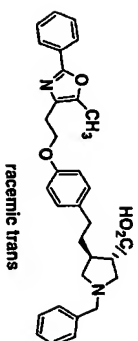
10

A solution of Part F compound (11.8 mg, 0.023

mmol) in 20% HCl:HOAc (1 mL of a 1:3 solution) was heated at 75°C for 3.5 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (Phenomenex Luna 5μ C18(2) 21.2 x 100 mm reverse phase column, 10 min continuous gradient from 30:70 A:B to 100% B according to the general procedure of Example 1) to afford the title compound (10.7 mg, 93%) as a colorless oil.  $[M + H]^+ = 511.4$

20

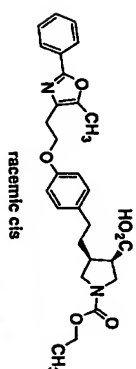
#### Example 341



25

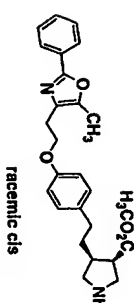
The title compound was prepared from the E-alkenyl ester Example 340 Part G compound (using the same procedure as for the synthesis of Example 340).  $[M + H]^+ = 511.4$

#### Example 342



5

A.

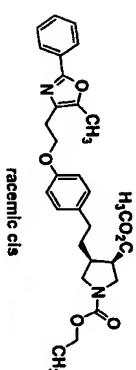


10

A mixture of Example 340 Part F compound (1.24 g, 2.36 mmol) and Pd black (164 mg) in 30% HCOOH-MeOH (12 mL) was stirred at RT for 16 h. The catalyst was filtered off; the filtrate was concentrated in vacuo, then partitioned between EtOAc and saturated aqueous NaHCO<sub>3</sub>. The aqueous layer was extracted with EtOAc (x 2) and the combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to yield Part A compound (983 mg; 2.26 mmol, 96%) as a colorless oil.  $[M + H]^+ = 435.4$

15

B.



20

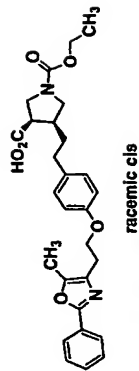
To a solution of Part A compound (20 mg, 0.11 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) was added Et<sub>3</sub>N (25 μL, 0.18 mmol) and ethyl chloroformate (20 μL, 0.21 mmol) and the mixture was stirred at RT for 2 h. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (Phenomenex Luna 5μ C18(2) 21.2 x 100 mm reverse phase column, 10 min continuous gradient from

25

20:80 A:B to 100% B according to the general procedure in Example 1).

$[M + H]^+ = 507.3$

5 C.

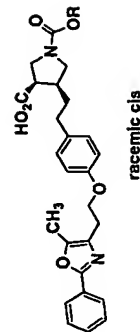


A solution of Part B compound in 20% HCl:HOAc (1 mL of a 1:3 solution) was heated at 75°C overnight, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (YMC ODS 20 x 100 mm reverse phase column, 10 min continuous gradient from 20:80 A:B to 100% B according to the procedure in Example 1) afforded the title compound (14.6 mg; 64% for 2 steps).

$[M + H]^+ = 493.5$

#### Examples 343-345

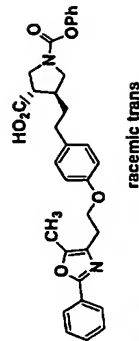
Examples 343-345 of the invention were prepared according to the general procedure described for the synthesis of Example 342 (using Example 342 Part A compound and appropriate chloroformates).



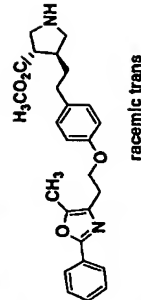
Example Number	R	$[M + H]^+$
343		521.5
344		541.5
345		559.5

5

#### Example 346



A.

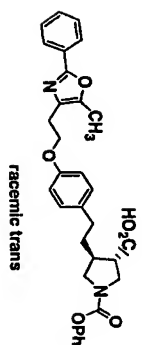


10

Part A compound was obtained by Pd black-catalyzed hydrogenolysis of Example 340 Part G compound following a procedure similar to Example 342 Part A.

15

B.

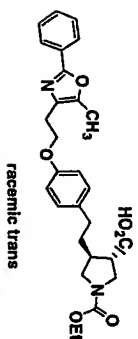


The title compound was prepared from Part A

5 compound according to the procedure described in Example 342.

$[M + H]^+ = 493.4$

#### Example 347



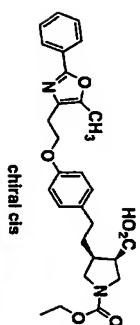
The title compound was obtained in a similar

manner as for Example 346 from Example 346 Part A

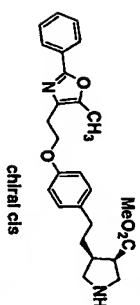
15 compound using ethyl chloroformate.

$[M + H]^+ = 541.4$

#### Example 348 (Enantiomer 1)



A.



The two enantiomers of racemic Example 342 Part A

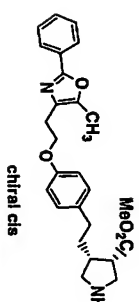
compound (800 mg) were separated by preparative HPLC:

Chiralpak AD chiral column; 5 cm x 50 cm, 20  $\mu$ ; isocratic

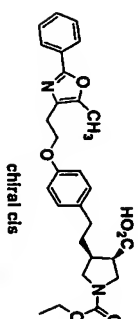
15% EtOH-MeOH (1:1) + 85% heptane + 0.1% Et<sub>3</sub>NH to afford

5 Part A compound (284 mg; faster-eluting enantiomer) and  
Part B compound (232 mg; slower-eluting enantiomer) as  
well as 71 mg of mixed fractions as colorless oils. The  
absolute stereochemistry of the two enantiomers is  
arbitrarily assigned.

B.



15 C



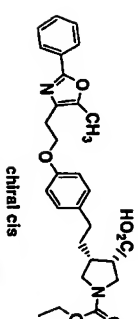
Example 348 was prepared according to the

procedure in Example 342 from ethyl chloroformate and

20 Part A compound.

$[M + H]^+ = 493.3$

#### Example 349 (Enantiomer 2)



25

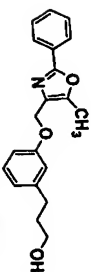




CH<sub>3</sub>CN (50 mL) was heated at 80°C for 16 h, then was cooled to RT and filtered. The filtrate was concentrated in vacuo and partitioned between EtOAc and H<sub>2</sub>O. The aqueous layer was extracted with EtOAc (x 2) and the combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to afford Part A compound (4.26 g, 68%) as a golden oil.

10 [M + H]<sup>+</sup> = 352.3

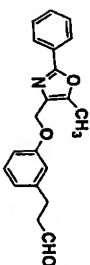
B.



15 To a 0° solution of Part B compound (4.3 g, 12.1 mmol) in THF (50 mL) was added LiAlH<sub>4</sub> (600 mg, 15.8 mmol) and the reaction was allowed to warm to RT and stirred at RT for 16 h. The mixture was then quenched cautiously with 1N aqueous HCl, extracted with EtOAc (x 2), washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient 100% hex to 100% EtOAc) to afford Part B compound (3.3 gm, 84%) as a colorless solid.

[M + H]<sup>+</sup> = 324.4

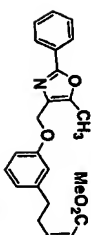
C.



20 To a dispersion of Dess-Martin reagent (5.0 g, 11.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was added a solution of Part B compound (3.3 g, 10.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (35 mL) dropwise at RT and the resulting mixture was allowed to stir at RT for 1 h. The mixture was then evaporated in vacuo and

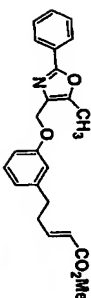
the residue was chromatographed (SiO<sub>2</sub>; 100% hex to 100% EtOAc) to yield Part C compound (2.69 g, 82%) as a golden oil.

5 D.

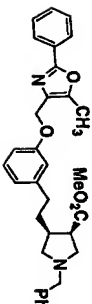


A suspension of NaH (50% dispersion in oil, 670 mg, 16.75 mmol) in THF (100 mL) was stirred at RT for 15 min and then cooled to -78°C. [Bis-(2,2,2-trifluoroethoxy)-phosphoryl]-acetic acid methyl ester (4.5 mL, 21.3 mmol) was added and the mixture was stirred for 20 min at -78°C. A solution of Part C compound (2.69 gm, 8.38 mmol) in THF (20 mL) was then added dropwise to the -78°C reaction. The reaction was allowed to warm to RT and stirred at RT for 16 h, then was quenched with aqueous NH<sub>4</sub>Cl. The aqueous phase was extracted with EtOAc (x 2); the combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc; 3 times) to afford Part D compound (Z-alkene; 2.22 g, 70%) and Part E compound (E-alkene; 0.346 g, 11%).

25 E.



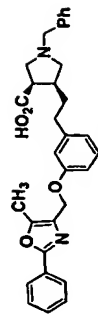
F.



To a solution of Part D compound (2.22 g, 5.88 mmol) in toluene (20 mL) was added Example 1 Part B compound (2.14 gm, 9 mmol) followed by TFA (5 drops). The mixture was stirred for 16 h at RT, evaporated in vacuo and the residue was chromatographed (SiO<sub>2</sub>; 100% hex to 100% EtOAc) to afford Part F compound (3.0 g, 100%) as a colorless oil.

$$[M + H]^+ = 511.6$$

10 G.



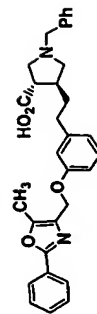
Racemic cis

A solution of Part F compound (51 mg, 0.1 mmol) in 20% HCl:HOAc (3 mL of a 1:3 solution) was heated at 70°C for 5 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (YMC ODS 20 x 100 mm reverse phase column, 10 min continuous gradient from 70:30 A:B to 100% B according to the general procedure in Example 1) to afford the title compound (0.8 mg, 1.6%) as a colorless oil.

$$[M + H]^+ = 497.4$$

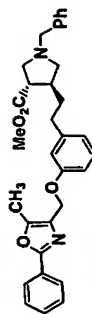
25

Example 353



Racemic cis

A.

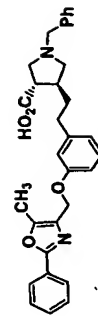


30

To a solution of Example 352 Part E compound (346 mg, 0.92 mmol) in toluene (5 mL) was added Example 1 Part B compound (387 mg, 1.63 mmol) followed by TFA (5 drops). The mixture was stirred for 16 h at RT, evaporated in vacuo and the residue was chromatographed (SiO<sub>2</sub>; 100% hex to 100% EtOAc) to afford Part A compound (414 mg, 88%) as a colorless oil.

$$[M + H]^+ = 511.6$$

10 B.

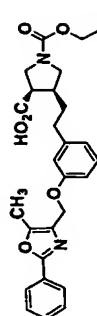


Racemic trans

A solution of Part A compound (16 mg, 0.03 mmol) in 20% HCl:HOAc (2 mL of a 1:3 solution) was heated at 70°C for 5 h, then was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (YMC ODS 20 x 100 mm reverse phase column, 10 min continuous gradient from 70:30 A:B to 100% B according to the general procedure in Example 1) to afford the title compound (1.5 mg, 10%) as a colorless oil.

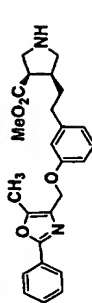
$$[M + H]^+ = 497.4$$

Example 354



Racemic cis

A.

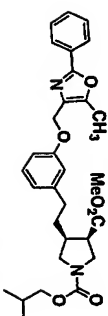


30

A mixture of Example 352 Part F compound (514 mg, 1 mmol) and Pd black (392 mg) in 30% HCO<sub>2</sub>H-MeOH (5 mL) was stirred at RT for 16 h. The reaction mixture was filtered, evaporated in vacuo and partitioned between EtOAc and saturated aqueous NaHCO<sub>3</sub>. The aqueous layer was extracted with EtOAc (x2) and the combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to yield crude Part A compound (369 mg; 0.88 mmol, 88%) as a colorless oil.

10 [M + H]<sup>+</sup> = 421.3

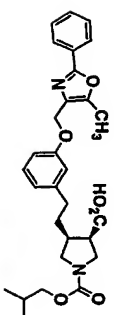
B.



15 To a solution of Part A compound (44 mg, 0.11 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added Et<sub>3</sub>N (50 μL, 0.36 mmol) and isobutyl chloroformate (35 μL, 0.27 mmol) and the mixture was stirred at RT for 1 h. The mixture was then evaporated in vacuo and purified by preparative HPLC (YMC ODS 20 x 100 mm reverse phase column, 10 min continuous gradient from 20:80 A:B to 100% B according to the general procedure described in Example 1) to give Part A compound.

[M + H]<sup>+</sup> = 521.5

C.



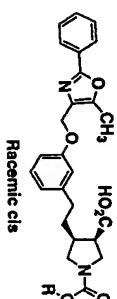
30 A solution of Part B compound in 20% HCl:HOAc (1 mL of a 1:3 solution) was heated at 70°C for 3 h, then was cooled to RT and concentrated in vacuo. The residue was

purified by preparative HPLC (YMC ODS 20 x 100 mm reverse phase column, 10 min continuous gradient from 30:70 A:B to 100% B according to the general procedure described in Example 1) to afford the title compound (3.3 mg; 6% for 2 steps) as a colorless oil.

[M + H]<sup>+</sup> = 507.5

#### Examples 355-357

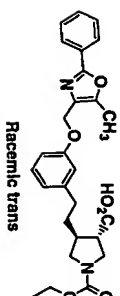
10 Examples 355-357 of the invention (cis-disubstituted pyrrolidine compounds) were prepared in the same manner as for Example 356:



Racemic cis

Example Number	R	[M + H] <sup>+</sup>
355		479.5
356		527.5
357		545.5

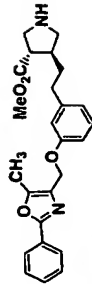
#### Example 358



Racemic trans

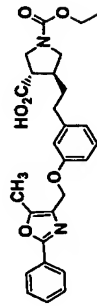
20

A.



A mixture of Example 353 Part A compound (395 mg, 0.78 mmol) in 30% HCOOH-MeOH (5 mL) and Pd black (318 mg) was stirred at RT under for 16 h. The reaction mixture was filtered; the filtrate was concentrated in vacuo and partitioned between EtOAc and saturated aqueous NaHCO<sub>3</sub>. The aqueous layer was extracted with EtOAc (x 2) and the combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give crude Part A compound (294 mg; 0.7 mmol, 90%) as a golden oil. [M + H]<sup>+</sup> = 421.3

15 B.



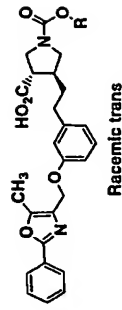
The title compound was prepared from Part A compound in the same manner as for the synthesis of Example 354 in 5% yield for 2 steps.

[M + H]<sup>+</sup> = 479.1

### Examples 359-361

The following compounds of the invention were prepared according to the same procedure as Example 354 starting from Example 358 Part A compound.

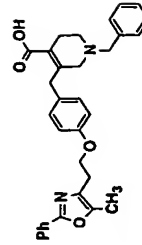
30



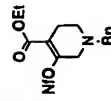
Example Number	R	[M + H] <sup>+</sup>
361		507.1
362		527.1
363		545.1

5

### Example 362



A.



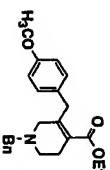
10

To a 0°C solution of ethyl 1-benzyl-3-oxo-4-piperidine carboxylate hydrochloride (5.0 g, 16.77 mmol) in MeOH (16 mL) was added aqueous K<sub>2</sub>CO<sub>3</sub> (2.55 g, 18.47 mmol; in 26 mL H<sub>2</sub>O). The mixture was stirred at 0°C for 10 min, then was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 X 30 mL). The

combined organic extracts were dried ( $K_2CO_3$ ) and concentrated in vacuo to give the corresponding free base (3.5 g, 80%). The  $\beta$ -keto ester free base (1.37 g, 5.22 mmol) was stripped from toluene (2x), dissolved in anhydrous THF (50 mL) and cooled to  $-70^\circ C$  under Ar.  $KN(TMS)_2$  in toluene (13.5 mL of a 0.5 M solution) was added dropwise. After stirring at  $-70^\circ C$  for 15 min, 1,1,2,2,3,3,4,4-Nonafluoro-1-butanefluoronyl fluoride (1.28 mL, 6.78 mmol) was added. The reaction was allowed to warm to RT and stirred overnight at RT, then was washed with saturated aqueous  $NH_4Cl$  (200 mL). The aqueous layer was extracted with  $Et_2O$  (3 X 50 mL). The combined organic extracts were dried ( $Na_2SO_4$ ) and concentrated in vacuo to give Part A compound as a brown oil (2.84 g, 100%), which was used in the next step without further purification.

[M + H] $^+$  = 544.4  
 $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.26 (m, 5 H), 4.21 (q, J = 7.0 Hz, 2 H), 3.59 (s, 2 H), 3.12 (s, 2 H), 2.58 (m, 2 H), 2.52 (m, 2 H), 1.24 (t, J = 7.0 Hz, 3H)

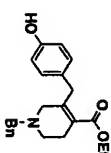
B.



To a solution of Bis(dibenzylideneacetone)palladium (0) [ $Pd(dba)_2$ ] (0.18 g, 0.31 mmol) and 1,1'-Bis(diphenylphosphino)ferrocene (dppf) (0.18 g, 0.31 mmol) in anhydrous THF (21 mL) under Ar was added 4-methoxybenzyl zinc chloride (25.0 mL, 11.5 mmol, 0.5 M in THF) at RT. The reagent mixture was stirred at RT for 20 min. A solution of Part A Compound (2.84 g, 5.22 mmol; stripped from anhydrous toluene 3x before use) in dry THF (20 mL) was added slowly to the Pd catalyst/organozinc reagent mixture. The mixture was heated at  $65^\circ C$  under Ar for 12 h, cooled to RT, and partitioned between  $CH_2Cl_2$  (70 mL)

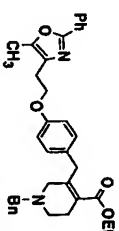
and saturated aqueous  $NaHCO_3$ . Solids were filtered off, and the aqueous phase was extracted with  $CH_2Cl_2$  (4 X 30 mL). The combined organic extracts were dried ( $K_2CO_3$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; 85:15 hexane: $EtOAc$ ) to afford Part B compound as a light yellow oil (1.37 g, 72%).  
 [M + H] $^+$  = 366.5

C.



To a  $0^\circ C$  solution of compound B (1.0 g, 2.74 mmol) in  $CH_2Cl_2$  (15 mL) was added dropwise  $BBr_3$  in  $CH_2Cl_2$  (6.5 mL of a 1.0 M solution; 6.49 mmol). The mixture was stirred at  $0^\circ C$  for 2 h.  $EtOH$  (1 mL) and saturated aqueous  $NaHCO_3$  (10 mL) were subsequently added to quench the reaction. The aqueous phase was further extracted with  $CH_2Cl_2$  (3 X 10 mL). The combined organic extracts were dried ( $Na_2SO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; 4:1 hex: $EtOAc$ ) to afford Part C compound (0.59 g, 61%) as light yellow solid.

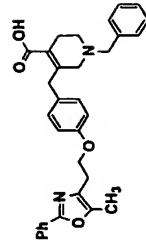
D.



Part C compound (0.264 g, 0.753 mmol) and Example 23 Part A compound (0.265 g, 0.942 mmol) were stripped from dry toluene (3x), then were dissolved in anhydrous MeCN (7.5 mL); finally anhydrous  $K_2CO_3$  (0.13 g, 0.942 mmol) was added. The reaction was stirred at  $90^\circ C$  overnight. Additional Example 23 Part A compound was

added until all Part C compound was consumed. Volatiles were removed in vacuo and the residue was dissolved in water (15 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 X 15 mL). The combined organic extracts were dried ( $\text{K}_2\text{CO}_3$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; 4:1 hex:EtOAc) to give compound D (0.202 g, 50%) as a light yellow oil.

E.

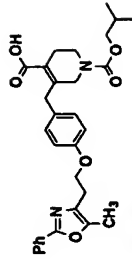


10

A solution of Part D compound in HCl/HOAc (1 mL of a conc. HCl:HOAc solution; 20:80 v/v) was heated at 90°C in a sealed tube for 8 h, then cooled to RT. Volatiles were removed in vacuo, and the residue was purified by preparative HPLC (YMC S5 ODS 20X250 mm column; continuous gradient from 50:50 solvent A:B to 100% solvent B; where solvent A = 90:10:0.1  $\text{H}_2\text{O}$ : $\text{CH}_3\text{CN}$ :TFA; solvent B = 90:10:0.1  $\text{CH}_3\text{CN}$ : $\text{H}_2\text{O}$ :TFA) and lyophilized from  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  to give the title compound (5.6 mg, 50%) as the TFA salt (light yellow oil).

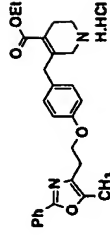
$[\text{M} + \text{H}]^+$  (electrospray) = 509.0

### Example 363



25

A.



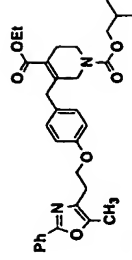
Example 362 Part D Compound (40 mg, 0.0745 mmol)

5 and Proton Sponge [1,8-bis(dimethylamino)naphthalene] (2.0 mg) were stripped from dry toluene (2x), then dissolved in  $\text{CH}_2\text{Cl}_2$  (1 mL). To this 0°C solution was added dropwise  $\alpha$ -chloroethyl chloroformate (21  $\mu\text{L}$ , 0.186 mmol). The reaction mixture was allowed to warm to RT, then heated at 40°C under Ar for 1 h. Volatiles were removed in vacuo; MeOH (1 mL) was added, and the mixture was heated at 50°C for 1 h, then cooled to RT. Volatiles were removed in vacuo to afford crude Part A compound as a light yellow oil, which was used in the next reaction without further purification.

$[\text{M} + \text{H}]^+ = 447.5$

15

B.



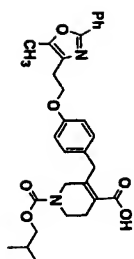
20

To a solution of Part A compound (ca 0.0745 mmol) in 1,4-dioxane/ $\text{H}_2\text{O}$  (2.0 mL of a 1:1 solution) were successively added isobutyl chloroformate (15.0  $\mu\text{L}$ , 0.064 mmol) and  $\text{NaHCO}_3$  (25.0 mg, 0.298 mmol). The mixture was stirred at RT for 1 h, then was partitioned between water (3 mL) and  $\text{CH}_2\text{Cl}_2$  (5 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (2 X 5 mL). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; 3:1 hex:EtOAc) to give Part B compound as a colorless oil (32.5 mg, 80%).

$[\text{M} + \text{H}]^+ = 547.2$

30

C.

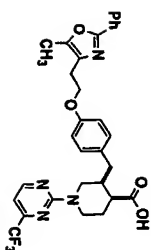


A solution of Part B Compound (32.5 mg, 0.0595

5 mmol) in 20% HCl/HOAc (2.0 mL of a conc HCl/HOAc solution; 20:80 v/v) was heated at 110°C in a sealed tube for 2 h, then cooled to RT. Volatiles were removed in vacuo, and the residue was purified by preparative HPLC (YMC S5 ODS 20 mm x 100 mm column; continuous gradient from 70% A:30 %B to 100% B for 10 min; flow rate = 20 mL/min, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and where B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give the title compound (15.4 mg; 50%) as a colorless solid.  
[M + H]<sup>+</sup> = 519.0

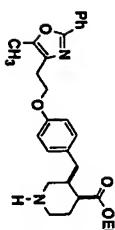
15

#### Example 364



20

A.



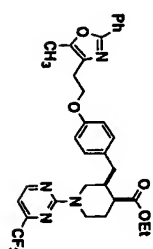
A mixture of Example 362 Part D Compound (0.26 g,

0.48 mmol) and 10% Pd/C (0.1 g) in HOAc (4.8 mL) was stirred overnight under an atmosphere of H<sub>2</sub> (60 psi pressure). The catalyst was filtered off, and the filtrate was concentrated in vacuo to afford crude Part A

compound as a light yellow oil (0.117 g, 54%), which was used in the next step without further purification.  
[M + H]<sup>+</sup> = 449.5

5

B.

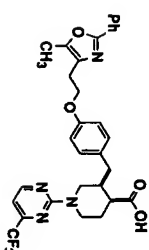


A mixture of Part A Compound (38.5 mg, 0.086 mmol), 2-Chloro-4-(trifluoromethyl)pyrimidine (21 μL, 0.172 mmol) and iPr<sub>2</sub>NEt (40 μL, 0.215 mmol) in dry toluene (1 mL) was heated at 100°C for 3 h. Volatiles were removed in vacuo, and the residue was purified by preparative HPLC (YMC S5 ODS 20 mm x 100 mm column; continuous gradient from 70% A:30 %B to 100% B for 10 min; flow rate = 20 mL/min, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and where B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give Part B compound (22.2 mg, 44% yield) as a white solid.  
[M + H]<sup>+</sup> = 595.6

15

20

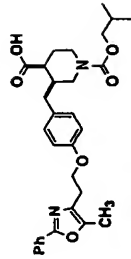
C.



Part B Compound (22.2 mg, 0.0373 mmol) was: 1)

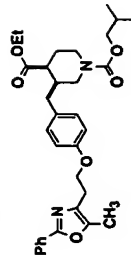
25 and 2) purified by preparative HPLC, both as for Example 363 Part C. The title compound was obtained as a white solid (12.6 mg, 60%).  
[M + H]<sup>+</sup> = 567.0



Example 365

5

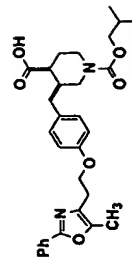
A.



To a solution of Example 364 Part A compound (35.5 mg, 0.0793 mmol) in 1,4-dioxane/H<sub>2</sub>O (2.0 mL of a 1:1 solution) were added isobutyl chloroformate (15.0  $\mu$ L, 0.111 mmol) and NaHCO<sub>3</sub> (27.0 mg, 0.317 mmol). The mixture was stirred at RT for 1 h, then water (3 mL) was added. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give crude Part A compound.

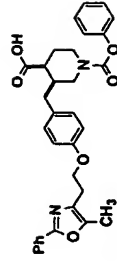
15

B.



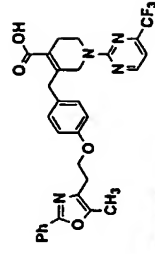
20

Crude Part A Compound was: 1) deprotected using the same HCl/HOAc/110°C procedure and 2) purified by preparative HPLC both as for Example 363 Part C. The title compound was obtained as a white solid (20.6 mg, 25 50% yield). [M + H]<sup>+</sup> = 521.1

Example 366

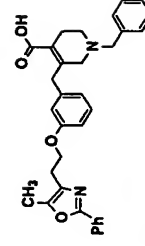
5

Example 364 Part A compound (20 mg, 0.045 mmol) was reacted with phenyl chloroformate (8.5  $\mu$ L, 0.067 mmol), followed by the acid-mediated hydrolysis of the ester (both steps as for Example 365) to give the title compound (12.0 mg, 50% yield) as a white solid.

10 [M + H]<sup>+</sup> = 541.0Example 367

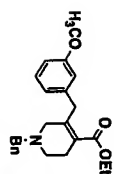
15

Example 363 Part A compound (76.7 mg; 0.171 mmol) was reacted with 2-chloro-4-(trifluoromethyl)pyrimidine (41.7  $\mu$ L; 0.342 mmol), followed by acid-mediated hydrolysis (both steps following the general procedures described in Example 365) to give the title compound (29 mg; 30%) as white solid.

20 [M + H]<sup>+</sup> = 565.0Example 369

25

A.



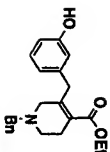
5 3-methoxybenzylzinc chloride (15 mL of a 0.5 M solution in THF, 7.47 mmol) was reacted with Example 362 Part A compound (1.85 g, 3.40 mmol) according to the general procedure described for the preparation of Example 362 Part B compound to give Part A compound (0.972 g, 78%) as a light yellow oil.

[M + H]<sup>+</sup> = 366.5

15 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.24-6.69 (m, 6 H), 6.66-6.63 (m, 3 H), 4.10 (q, J = 7.1 Hz, 2 H), 3.69 (s, 3 H), 3.68 (s, 2 H), 3.41 (s, 2 H), 2.90 (s, 2 H), 2.46-2.40 (m, 4 H), 1.16 (t, J = 7.1 Hz, 3 H)

<sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 167.6, 159.5, 145.0, 140.7, 137.7, 129.1, 128.8, 128.1, 127.0, 124.1, 121.0, 114.3, 111.3, 61.7, 60.1, 56.8, 55.0, 48.9, 38.1, 26.9, 14.1

20 B.

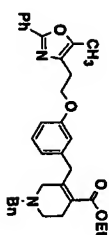


Part A Compound was subjected to BBr<sub>3</sub> deprotection using the general procedure described for Example 362

25 Part C compound. Part B compound (42%) was isolated as a brown oil.

[M + H]<sup>+</sup> = 352.4

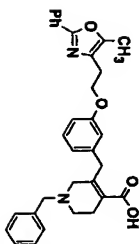
C.



5 Part C compound was prepared from Part B compound as a light yellow oil (50%) following the general procedure described for the synthesis of Example 362 Part D compound.

[M + H]<sup>+</sup> = 537.7

10 D.

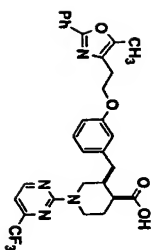


The title compound was obtained from Part C compound following the general procedure described in Example 362 Part E compound. The title compound (50%) was obtained as a brown solid.

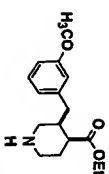
[M + H]<sup>+</sup> = 509.0

20

#### Example 370



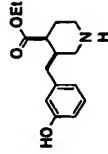
A.



25

A mixture of Example 369 Part A compound (0.824 g, 2.25 mmol) and 10% Pd-C (1.65 g) in HOAc (23 mL) was stirred overnight under an atmosphere of H<sub>2</sub> (80 psi pressure). The catalyst was filtered off and volatiles were removed in vacuo to give Part A compound as a brown oil, which was used in the next step without further purification.

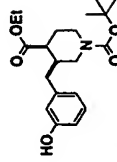
B.



10

To a 0°C solution of crude Part A compound in CH<sub>2</sub>Cl<sub>2</sub> (23 mL) was added BBr<sub>3</sub> (11.7 mL, 11.7 mmol, 1 M in CH<sub>2</sub>Cl<sub>2</sub> added slowly over 15 min. The reaction was stirred at 0°C for 1 h, then was quenched with MeOH (1 mL) and saturated aqueous NaHCO<sub>3</sub> (10 mL). The organic layer was separated; the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 15 mL). The combined organic extracts were concentrated in vacuo to give crude Part B compound as a brown oil.

C.



25

To a solution of Part B compound in 1,4-dioxane-H<sub>2</sub>O (20 mL, 1:1 v/v) was added di-tert-butyl dicarbonate (0.419 g, 1.91 mmol) and NaHCO<sub>3</sub> (0.322 g, 3.83 mmol). The mixture was stirred at RT for 1 h, then was partitioned between H<sub>2</sub>O and EtOAc (15 mL each). The aqueous layer was extracted with EtOAc (2 x 15 mL) and the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was chromatographed

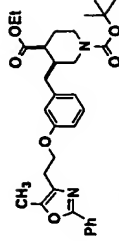
- 428 -

(SiO<sub>2</sub>; stepwise gradient from 4:1 to 65:35 hex:EtOAc) to give the title compound as a colorless oil (0.413 g, 51% yield over 3 steps).

[M + H]<sup>+</sup> = 364.4

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.05 (t, J = 7.5 Hz, 1 H), 6.65-6.61 (m, 3 H), 4.11 (m, 2 H), 3.92 (m, 1 H), 3.78 (m, 1 H), 2.90-2.86 (m, 2 H), 2.60-2.17 (m, 4 H), 1.75 (m, 2 H), 1.38 (s, 9 H), 1.23 (t, 7.1 Hz, 3 H)

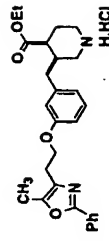
10 D.



Part C compound (0.413 g, 1.13 mmol) and 2-(5-

methyl-2-phenyloxazole-4-yl)ethanol (0.255 g, 1.25 mmol) were stripped from dry toluene (3x). To a mixture of these two compounds in dry toluene (12 mL) was added Bu<sub>3</sub>PCHN (0.302 g, 1.25 mmol). The mixture was heated at 50°C under Ar for 2 h, cooled to RT and volatiles were removed in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 5:1 to 7:3 hex:EtOAc) to give Part D compound as a colorless oil (0.370 g, 60%).

E.



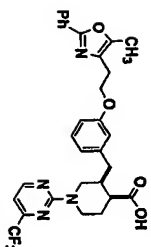
25

To a 0°C solution of MeOH (4.0 mL) was slowly added acetyl chloride (1.2 mL). The mixture was stirred at 0°C for 1 h, then was added to Part D compound (50 mg, 0.091 mmol). The mixture was stirred at 0°C for 15 min and then was allowed to warm to RT. Volatiles were removed in vacuo to give crude Part E compound (41.1 mg, 93%),

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which was used in the next reaction without further purification.  $[M + H]^+ = 449.5$

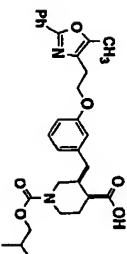
3



Part E compound was reacted with 2-chloro-4-(trifluoromethyl)pyrimidine using the procedure described in Example 364. The crude product from this reaction was subjected to acid-mediated hydrolysis and preparative HPLC (as for Example 363) to afford the title compound as a white solid (27% for 2 steps).  $[M + H]^+ = 567.4$

15

### Example 371



20 \_\_\_\_\_

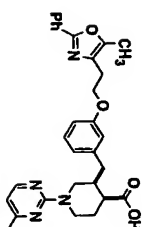
Example 370 Part E compound was reacted with isobutyl chloroformate followed by acid-mediated hydrolysis and preparative HPLC purification (as described for Example 365) to afford the title compound as a white solid.

25 Example 365 to afford the title compound as a white solid.

[M + H]<sup>+</sup> = 521.3

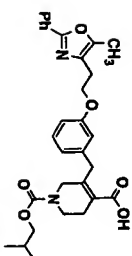
- 430 -

Example 372

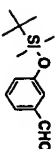


5 Example 370 Part E compound was reacted with 2-chloro-4-methylpyrimidine (Example 174 Part A compound) according to the general procedure described in Example 364 Part B compound. The crude product was subjected to acid hydrolysis and HPLC purification (as for Example 363) to afford the title compound as a white solid (30% yield for two steps).  $[M + H]^+ = 513.4$

### Example 373



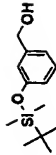
A.



20 A mixture of 3-hydroxybenzaldehyde (3.59 g, 28.51 mmol), *t*-butyldimethylsilyl chloride (5.1 g, 32.79 mmol) and imidazole (3.92 g, 57.02 mmol) in DMF (50 mL) was stirred at RT for 2 h, then was partitioned between saturated aqueous  $\text{NH}_4\text{Cl}$  (100 mL) and  $\text{Et}_2\text{O}$  (50 mL). The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (2 x 50 mL); the combined organic extracts were washed with  $\text{H}_2\text{O}$  (2 x 50 mL), brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo to afford Part A Compound as a yellow oil (6.74 g, 100% yield).

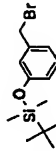
- 431 -

B.



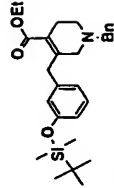
To a 0°C solution of Part A compound (6.74 g; 28.5 mmol) in MeOH (100 mL) was added NaBH<sub>4</sub> (2.37 g, 62.7 mmol) portionwise over 10 min, and the reaction was stirred at 0°C for 1 h. Saturated aqueous NH<sub>4</sub>Cl (100 mL) was added, and the mixture was extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with H<sub>2</sub>O (2 X 50 mL), brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo to afford Part B compound as a yellow oil (7.41 g, 100%).

C.



To a 0°C solution of Part B compound (7.41 g; 28.5 mmol) and Ph<sub>3</sub>P (9.44 g, 35.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (56 mL) was added CBr<sub>4</sub> (11.94 g, 35.6 mmol) portionwise over 10 min. The mixture was warmed to RT over 40 min, then was concentrated to 1/5 of the original volume and hexane (60 mL) was added. The precipitate was filtered off and rinsed with hexane. The combined filtrate and rinses were concentrated in vacuo, and the residue was chromatographed (SiO<sub>2</sub>; 95:5 hex:EtOAc) to give Part C compound (10.2 g, 100%) as a colorless oil.

D.



To a 0°C solution of Rieke zinc (23 mL of an activated zinc powder suspension in THF [containing 5 g of Zn per 100 mL THF], 17.8 mmol) in THF (18 mL) was

added a solution of Part C compound (4.10 g, 13.7 mmol) in THF (18 mL) under Ar. The mixture was stirred at RT for 3 h; excess zinc was filtered off under Ar and the benzylzinc solution was added to a mixture of 1.1'-

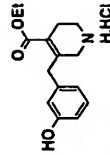
5 Bis(diphenylphosphino)ferrocene (dppf) (0.156 g, 0.274 mmol) and Bis(dibenzylideneacetone)palladium (0) [Pd(dba)<sub>2</sub>] (0.157 g, 0.274 mmol) under Ar. The mixture was stirred at RT for 30 min, after which a solution of Example 362 Part A compound (2.47 g, 4.56 mmol) in THF (18 mL) was added dropwise. The mixture was heated to 65°C for 12 h, then cooled to RT. Saturated aqueous NaHCO<sub>3</sub> (60 mL) was added; solids were filtered off, and the cake was rinsed with Et<sub>2</sub>O. The aqueous phase was extracted with Et<sub>2</sub>O (3 X 30 mL). The combined organic extracts/rinses were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuo, and chromatographed (SiO<sub>2</sub>; 85:15 hexane:EtOAc) to afford Part D compound as a light yellow oil (0.982 g, 46%).

[M + H]<sup>+</sup> = 466.7

20 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.17 (m, 5 H), 7.02 (t, J = Hz, 1 H), 6.70 (m, 1 H), 6.60 (m, 2 H), 4.11 (q, J = 7.0 Hz, 2 H), 3.66 (s, 2 H), 3.40 (s, 2 H), 2.88 (s, 2 H), 2.60-2.39 (m, 4 H), 1.15 (t, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.10 (s, 6 H)

25 <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 167.7, 155.6, 145.2, 140.6, 137.9, 129.1, 128.8, 128.1, 121.7, 120.2, 117.8, 61.8, 60.1, 57.0, 49.0, 38.0, 27.0, 25.7, 18.2, 14.2

E.

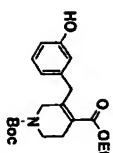


30

To a 0°C solution of Part D compound (0.391 g, 0.842 mmol) and Proton-sponge (3 mg) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was slowly added α-chloroethyl chloroformate (0.233 mL, 2.10 mmol). The mixture was heated at 40°C for 1 h; volatiles were

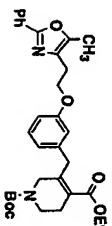
removed in vacuo, and a solution of the residue in MeOH (8 mL) was heated at 40°C for 1 h. Volatiles were removed in vacuo to afford Part E compound as a yellow oil, which was used in the next reaction without further purification.  $[M + H]^+ = 261.3$

## F.



To a solution of compound E in 1,4-dioxane/H<sub>2</sub>O (10 mL of a 1:1 v/v solution) was added di-tert-butyl dicarbonate (0.165 g, 0.758 mmol) and NaHCO<sub>3</sub> (0.212 g, 2.53 mmol). The mixture was stirred at RT for 2 h, then was partitioned between H<sub>2</sub>O (20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (2 X 15 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 X 15 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuo, and chromatographed (SiO<sub>2</sub>; 4:1 hex:EtOAc) to give Part F compound as a colorless oil (0.218 g, 72% yield over 2 steps).  $[M + H]^+ = 362.4$

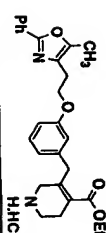
## G.



Part F Compound (0.218 g, 0.603 mmol) and 2-(5-methyl-2-phenylloxazole-4-yl)ethanol (0.184 g, 0.904 mmol) were stripped from dry toluene (3x), then were dissolved in dry toluene (6 mL). Bu<sub>3</sub>PCHCN (0.20 mL, 0.905 mmol) was added dropwise and the mixture was heated at 60°C under Ar for 2 h, then was cooled to RT. Volatiles were removed in vacuo, and the residue was chromatographed (SiO<sub>2</sub>; gradient from 5:1 to 7:3 hex:EtOAc) to afford Part G compound as a colorless oil (0.297 g, 90%).  $[M + H]^+ = 547.7$

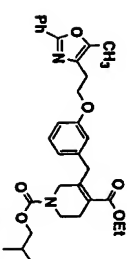
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## H.



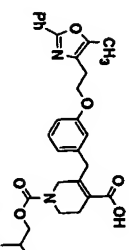
Part G compound was deprotected (removal of N-Boc group) using the AcCl/MeOH procedure described in Example 370 (Part E) to give Part H compound (0.263 g; 100% yield) as an oil.  $[M + H]^+ = 447.5$

## I.



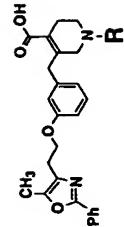
Part H compound (39.1 mg; 0.081 mmol) was reacted (as for Example 363) with isobutyl chloroformate (11.6 µL, 0.090 mmol) to give compound I (44.5 mg; 100%) as a light yellow oil, which was used in the next reaction without further purification.  $[M + H]^+ = 547.6$

## J.



Part I Compound (22.2 mg; 0.040 mmol) was hydrolyzed under acid (20% HCl/HOAc) conditions as described in Example 362 Part E. The crude product was purified by preparative HPLC (XMC S5 ODS 20 X 250 mm column; continuous gradient from 50:50 solvent A:B to 100% solvent B; where solvent A = 90:10:0.1 H<sub>2</sub>O:CH<sub>3</sub>CN:TFA; solvent B = 90:10:0.1 CH<sub>3</sub>CN:H<sub>2</sub>O:TFA) to afford the title compound (38%) as a white solid.  $[M + H]^+ = 519.2$

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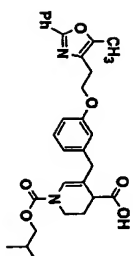
Example No	R	[M + H] <sup>+</sup>
374		539.2
375		491.2
376		565.0
377		553.2
378		569.1
379		505.1
380		519.6

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.96 (m, 2 H), 7.47 (m, 3 H), 7.16 (t, J = 7.4 Hz, 1 H), 6.83-6.80 (m, 3 H), 4.21 (t, J = 6.7 Hz, 2 H), 3.89-3.50 (m, 8 H), 2.97 (t, J = 6.7 Hz, 2 H), 2.47 (s, 2 H), 2.38 (s, 3 H), 2.00-1.60 (m, 1 H), 0.92-0.71 (br., 6 H)

<sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD) δ 169.2, 159.5, 158.5, 155.3, 140.1, 131.6, 130.2, 129.1, 128.5, 125.7, 124.6, 120.9, 114.8, 112.1, 71.4, 66.0, 46.3, 40.0, 37.2, 27.5, 26.0, 25.6, 18.4, 9.6

# Examples 374-380

Examples 374-380 of the invention were prepared according to the general procedures described for the syntheses of Examples 363, 364, 370 and 373.

Example 381

5 A solution of Example 373 Part I compound (24 mg, 0.044 mmol), LiOH.H<sub>2</sub>O (4.2 mg, 0.175 mmol) and MeOH (1 drop) in THF-H<sub>2</sub>O (1.5 mL, 2:1 v/v) was stirred at RT for 3 h. The reaction was acidified to pH 2 with 1 N aqueous HCl, then was extracted with EtOAc (3 x 5 mL). The combined organic extracts were concentrated in vacuo and the residue was purified by preparative HPLC (YMC S5 ODS 20X250 mm column; continuous gradient from 50:50 solvent A:B to 100% solvent B; where solvent A = 90:10:0.1 H<sub>2</sub>O:CH<sub>3</sub>CN:TFA; solvent B = 90:10:0.1 CH<sub>3</sub>CN:H<sub>2</sub>O:TFA) to give the title compound (11.9 mg, 52%) as a white solid.

[M + H]<sup>+</sup> = 519.2

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.95 (m, 2 H), 7.46 (m, 3 H), 7.18 (t, J = 7.9 Hz, 1 H), 6.85-6.66 (m, 4 H), 4.22 (br. s, 2 H), 4.95-4.85 (m, 3 H), 3.40 (m, 3 H), 2.98 (t, J = 6.6 Hz, 2 H), 2.90 (m, 1 H), 2.38 (s, 3 H), 2.10-1.73 (m, 3 H), 0.94 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H)

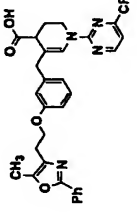
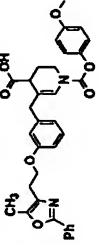
<sup>13</sup>C NMR (125.7 MHz, DMSO-d<sub>6</sub>, t = 100°C) δ 174.4, 159.2, 159.0, 153.2, 145.2, 141.5, 133.4, 130.3, 129.7, 129.3, 128.0, 126.1, 123.7, 121.9, 116.0, 115.3, 113.1, 71.9, 70.0, 40.7, 40.2, 39.6, 28.0, 26.4, 25.0, 19.2, 10.2

Examples 382-389

30 Examples 382-389 of the invention were prepared according to the procedures described for the synthesis of Example 373 and Example 381.

Example No.	Structure	[M + H] <sup>+</sup>
382		477.0
383		491.2
384		505.1
385		519.1
386		533.1
387		553.2

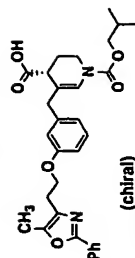


Example No.	Structure	[M + H] <sup>+</sup>
388		565.1
389		569.1

arbitrarily assigned): retention time = 60 min; 17.6 mg, white solid, 70% recovery, >99% e.e.). [M + H]<sup>+</sup> = 519.2, [α]<sub>D</sub><sup>20</sup> = +100.3° (c = 0.50 g/100 mL, MeCN)

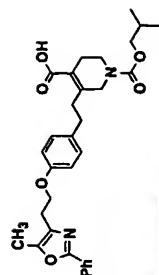
5

## Example 391



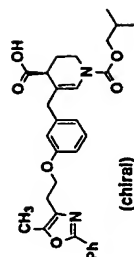
10

## Example 392



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## Example 390



The two individual enantiomers of Example 381 (racemate; 50 mg) were separated by preparative HPLC (Chiralpak<sup>®</sup> AD Chiral column; 5 cm X 50 cm, 20 μ, Chiral Technologies Inc; isocratic solvent system: 6% i-PrOH/heptane; Flow rate = 40 mL/min). The faster eluting fraction (single enantiomer) was characterized as Example 390 (absolute stereochemistry arbitrarily assigned): retention time = 45 min; 22.5 mg, white solid, 90% recovery, >99% e.e., [M + H]<sup>+</sup> = 519.2, [α]<sub>D</sub><sup>20</sup> = -108.8° (c = 0.358 g/100 mL, MeCN).

15

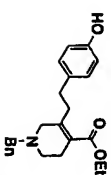
To a 0°C solution of ZnCl<sub>2</sub> in THF (12.65 mL of a 1 M solution, 12.65 mmol) was added 4-methoxyphenethyl magnesium chloride in THF (19.5 mL of a 0.5 M solution, 9.73 mmol) dropwise. After stirring for 40 min at 0°C, bis(dibenzylideneacetone)palladium (0) [Pd(dba)<sub>3</sub>] (0.153 g, 0.265 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (dppf) (0.152 g, 0.265 mmol) were added. The reagent mixture was stirred at RT for 10 min, after which a solution of Example 362 Part A compound (2.4 g, 4.42 mmol) in THF (18 mL) was added dropwise. The reaction was heated at 65°C for 12 h, then cooled to RT and concentrated in vacuo. The residue was partitioned

25

between  $\text{CH}_2\text{Cl}_2$  (80 mL) and saturated aqueous  $\text{NaHCO}_3$  (40 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (4 X 30 mL). The combined organic extracts were dried ( $\text{K}_2\text{CO}_3$ ), concentrated in vacuo and the residue was chromatographed (SiO<sub>2</sub>; 85:15 hex:EtOAc) to afford Part A compound as a light yellow oil (0.989 g, 59%). [M + H]<sup>+</sup> = 380.5

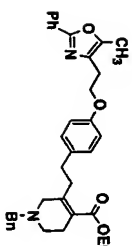
<sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.24 (m, 5 H), 7.15 (d, J = 7.9 Hz, 2 H), 6.83 (d, J = 7.4 Hz, 2 H), 4.21 (q, J = 7.0 Hz, 2 H), 3.76 (s, 3 H), 3.58 (s, 2 H), 3.03 (s, 2 H), 2.73-2.47 (m, 8 H), 1.30 (t, J = 7.0 Hz, 3 H)

B.



To a 0°C solution of Part A compound (0.483 g, 1.273 mmol) in  $\text{CH}_2\text{Cl}_2$  (13 mL) was added dropwise  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  (3.2 mL of a 1.0 M solution; 3.20 mmol). The mixture was stirred at 0°C for 1.5 h. EtOH (1 mL) and saturated aqueous  $\text{NaHCO}_3$  (10 mL) were subsequently added to quench the reaction. The aqueous phase was further extracted with  $\text{CH}_2\text{Cl}_2$  (3 X 10 mL). The combined organic extracts were dried  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 3:1 hex:EtOAc) to afford Part B compound (0.443 g, 95%) as a light yellow solid.

C.

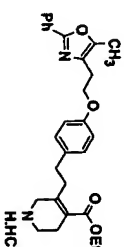


Part B compound (0.443 g, 1.212 mmol) and Example 23 Part A compound (0.426 g, 1.516 mmol) were stripped from dry toluene (3x), then were dissolved in anhydrous

- 442 -

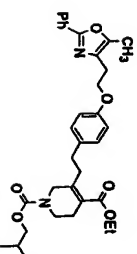
MeCN (12 mL) and anhydrous  $\text{K}_2\text{CO}_3$  (0.503 g, 3.63 mmol) was added. The reaction mixture was stirred at 90°C overnight. Additional Example 23 Part A compound (0.341 g, 1.21 mmol) was added, and the reaction was kept at 90°C for another 4 h. Volatiles were removed in vacuo, and the residue was dissolved in water (15 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3 X 15 mL). The combined organic extracts were dried ( $\text{K}_2\text{CO}_3$ ) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 4:1 hex:EtOAc) to afford Part C compound (0.400 g, 60%) as a light yellow oil.

D.



Part C Compound (0.216 g, 0.394 mmol) and Proton Sponge (1,8-bis(dimethylamino)naphthalene) (4.0 mg) were stripped from dry toluene (2x), then dissolved in  $\text{CH}_2\text{Cl}_2$  (4 mL). To this 0°C solution was added dropwise  $\alpha$ -chloroethyl chloroformate (0.10 mL, 0.906 mmol). The reaction was allowed to warm to RT, then heated to 40°C under Ar for 1h. Volatiles were removed in vacuo; MeOH (4 mL) was added, and the mixture was heated at 50°C for 1 h. Volatiles were removed in vacuo to afford crude Part D compound (0.156 g, 80% yield) as a light yellow oil, which was used in the next step without further purification. [M + H]<sup>+</sup> = 461.5

E.



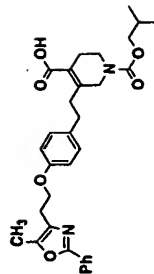
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Part E compound was prepared from Part D compound and isobutyl chloroformate according to the procedure described for the synthesis of Example 363 Part B compound.

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F.

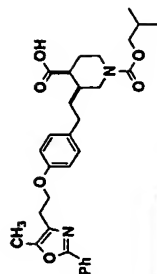


The title compound (white solid; 60% overall for 2 steps) was prepared from Part E compound by acid-mediated hydrolysis followed by purification by preparative HPLC according to the procedure described for the synthesis of Example 363.

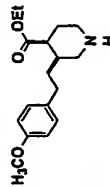
$[M + H]^+ = 533.5$

15

#### Example 393



A.

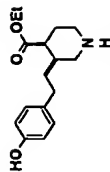


20

A mixture of Example 392 Part A Compound (0.506 g, 1.33 mmol) and 10% Pd/C (1.02 g) in HOAc (14 mL) was stirred under an atmosphere of  $H_2$  (80 psi pressure) overnight, after which the catalyst was filtered off. The filtrate was concentrated in vacuo to give crude Part A compound as a brown oil.

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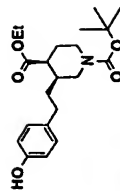
B.



To a 0°C solution of crude Part A compound in  $CH_2Cl_2$  (13 mL) was added  $BBR_3$  (4.0 mL, 4.0 mmol, 1 M in  $CH_2Cl_2$ ) dropwise over ~15 min. The mixture was stirred at 0°C for 1 h. MeOH (1 mL) and saturated aqueous  $NaHCO_3$  (10 mL) was added slowly to quench the reaction, which was partitioned between water and  $CH_2Cl_2$ . The aqueous layer was extracted with  $CH_2Cl_2$  (2 X 15 mL). The combined organic extracts were concentrated under reduced pressure to afford crude Part B compound as a brown oil.

10

C.

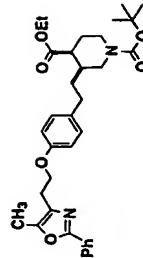


15

A solution of crude Part B compound, di-tert-butyl dicarbonate (0.291 g, 1.334 mmol) and  $NaHCO_3$  (0.448 g, 5.33 mmol) in 1,4-dioxane- $H_2O$  (13.4 mL, 1:1 v/v) was stirred at RT for 1 h, then was partitioned between  $H_2O$  and EtOAc (15 mL each). The aqueous phase was extracted with EtOAc (2 X 15 mL). The combined organic extracts were dried ( $Na_2SO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; 7:3 hex:EtOAc) to give Part C compound as a white solid (0.277 g, 55% yield over 3 steps).

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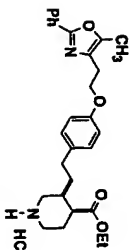
D.



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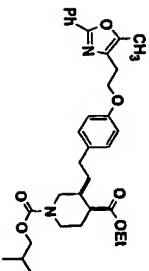
Part C Compound (0.277 g, 0.734 mmol) and 2-(5-methyl-2-phenyloxazole-4-yl)ethanol (0.224 g, 1.102 mmol) were stripped from dry toluene (3x), then were dissolved in dry toluene (7.4 mL) and Bu<sub>4</sub>PtCHN (0.266 g, 1.102 mmol) was added. The mixture was heated at 50°C under Ar for 2 h, then cooled to RT and volatiles were removed in vacuo. The residue was purified (SiO<sub>2</sub>; 3:1 hex:EtOAc) to give Part D compound as a colorless oil (0.373 g, 90%).

10 E.



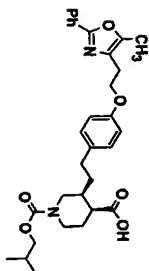
The deprotection of the N-Boc group of Part D compound (64 mg, 0.114 mmol) was carried out using the AcCl/MeOH procedure described for the synthesis of Example 370 Part E compound to give Part E compound (56.7 mg, 100%) as an oil.

20 F.



Part F compound was prepared from Part E compound and isobutyl chloroformate according to the procedure described for the synthesis of Example 363 Part B compound.

G.



The title compound (white solid) was prepared from Part F compound by acid-mediated hydrolysis and purified by preparative HPLC according to the procedure described for the synthesis of Example 363.  
[M + H]<sup>+</sup> = 535.4

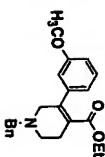
10 Examples 394-399

Examples 394-399 of the invention were prepared according to the procedures described for the synthesis of Example 392 and Example 393. The N-pyrimidine compounds were synthesized using the procedure described for the synthesis of Example 364 Part B compound.

Example No.	Structure	[M + H] <sup>+</sup>
394		553.5
395		579.5



A.

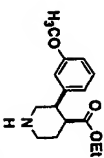


Example 362 Part A compound (1.93 g, 3.55 mmol) was reacted with 3-methoxyphenyl magnesium chloride (7.8 mL, 1 M solution in THF, 7.8 mmol) according to the procedure described in Example 392 Part A to give Part A compound (0.745 g, 60%) as a light yellow oil.

$[M + H]^+ = 352.4$

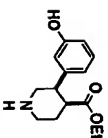
$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.38-7.27 (m, 6 H), 6.82 (m, 1 H), 6.75-6.70 (m, 2 H), 3.93 (q,  $J = 7.1$  Hz, 2 H), 3.77 (s, 3 H), 3.67 (s, 2 H), 3.28 (s, 2 H), 2.80-2.56 (m, 4 H), 0.90 (t,  $J = 7.1$  Hz, 3 H)  
 $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  168.1, 159.1, 144.4, 141.8, 137.3, 129.7, 129.0, 128.8, 128.2, 127.1, 125.5, 119.5, 112.8, 112.7, 61.8, 59.9, 58.1, 55.0, 48.8, 26.7, 13.4

B.



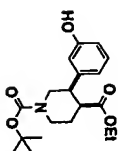
A mixture of Part A compound (0.241 g, 0.687 mmol) and 10% Pd/C (0.48 g) in HOAc (10 mL) mixture was stirred under an atmosphere of  $H_2$  (80 psi) for 24 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo to give crude Part B compound as a brown oil.

C.



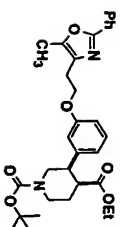
To a 0°C solution of crude Part B compound in  $CH_2Cl_2$  (6.8 mL) was slowly added  $EtBr$  (3.41 mL, 3.41 mmol, 1 M in  $CH_2Cl_2$ ) over 15 min. The mixture was stirred at 0°C for 1 h. MeOH (1 mL) and saturated aqueous  $NaHCO_3$  (10 mL) were slowly added to quench the reaction. The aqueous layer was extracted with  $CH_2Cl_2$  (3 X 10 mL). The combined organic extracts were concentrated in vacuo to give crude Part C compound as a brown oil.

D.



A solution of crude Part C compound, di-tert-butyl dicarbonate (0.151 g, 0.687 mmol) and  $NaHCO_3$  (0.230 g, 2.74 mmol) in 1,4-dioxane- $H_2O$  (4.0 mL, 1:1 v/v) was stirred at RT for 1 h.  $H_2O$  (15 mL) was added and the mixture was extracted with  $EtOAc$  (3 X 10 mL). The combined organic extracts were dried ( $Na_2SO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; 3:1 hex:EtOAc) to give Part D compound as a colorless oil (0.106 g, 45% yield over 3 steps).

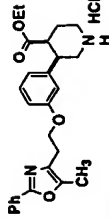
E.



Part D Compound (0.105 g, 0.300 mmol) and 2-(5-methyl-2-phenylloxazole-4-yl)ethanol (0.092 g, 0.450 mmol) were stripped from dry toluene (3X), then were dissolved in dry toluene (3.0 mL) and  $Bu_4PCHCN$  (0.108 g, 0.450 mmol) was added. The mixture was heated at 50°C under Ar for 2 h, then cooled to RT and concentrated in vacuo.

The residue was chromatographed (SiO<sub>2</sub>; 3:1 hex:EtOAc) to give Part E compound as a colorless oil (0.119 g, 75%).

F.



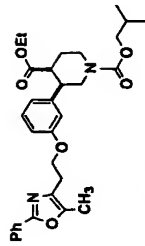
5

To MeOH (12.5 mL) at 0°C was slowly added acetyl chloride (3.2 mL). The solution was stirred 0°C for 1 h, then was added to Part E compound (0.119 g, 0.223 mmol).

The mixture was stirred at 0°C for 15 min and then gradually warmed to RT. Volatiles were removed in vacuo to give crude Part F compound (99.9 mg, 95%), which was used in the next reaction without further purification. [M + H]<sup>+</sup> = 435.5

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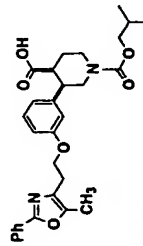
G.



Part G compound was prepared from Part F compound and isobutyl chloroformate according to the procedure described for the synthesis of Example 363 Part B compound.

20

H.



25

The title compound (white solid) was prepared from Part G compound by acid-mediated hydrolysis and purified

by preparative HPLC according to the procedure described for the synthesis of Example 363. [M + H]<sup>+</sup> = 507.2

5

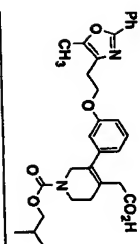
# Examples 403-405

Examples 403-405 of the invention were prepared according to the procedures described for the synthesis of Example 402. The N-pyrimidine compounds were synthesized using the procedure described for the synthesis of Example 364 Part B compound.

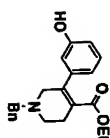
10

Example No.	Structure	[M + H] <sup>+</sup>
403		527.2
404		553.2
405		499.2

15

Example 406

A.



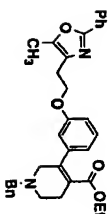
5

To a solution of Example 362 Part A Compound (1.68 g, 3.11 mmol) and 3-hydroxyphenylboronic acid (0.86 g, 6.22 mmol) in 1,4-dioxane (31 mL) were added Pd(PPh<sub>3</sub>)<sub>4</sub> (1.08 g, 0.933 mmol), LiCl (0.263 g, 6.21 mmol), and aqueous K<sub>2</sub>CO<sub>3</sub> (3.1 mL of a 2 M solution, 6.21 mmol). The mixture was heated at 115°C under Ar for 12 h, then was cooled to RT. Precipitates were filtered off. H<sub>2</sub>O (40 mL) was added, and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic extracts were dried (NaHCO<sub>3</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 7:3 hex:EtOAc) to give Part A compound (1.03 g, 95%) as a colorless oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.33 (br s, 1 H), 7.37-6.34 (m, 9 H), 3.85 (q, t = 7.0 Hz, 2 H), 3.70 (s, 2 H), 3.24 (s, 2 H), 2.76 (m, 2 H), 2.62 (m, 2 H), 0.83 (t, J = 7.0 Hz, 3 H)

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 168.3, 156.2, 144.2, 141.3, 135.4, 129.7, 129.2, 128.3, 127.6, 125.4, 118.7, 115.0, 114.0, 107.5, 103.0, 61.9, 60.3, 57.3, 48.8, 26.0, 13.3

B.

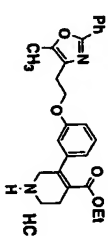


- 454 -

Part A compound (1.0 g, 2.97 mmol) and Example 23 Part A compound (1.04 g, 3.70 mmol) were stripped from dry toluene (3x), then were dissolved in anhydrous MeCN (30 mL); finally anhydrous K<sub>2</sub>CO<sub>3</sub> (1.64 g, 11.86 mmol) was added. The reaction was stirred at 90°C overnight. More Example 23 Part A compound (0.416 g, 1.48 mmol) was added and the mixture was stirred at 90°C for another 4 h. Volatiles were removed in vacuo, and the residue was dissolved in water (30 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic extracts were dried (K<sub>2</sub>CO<sub>3</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 7:3 hex:EtOAc) to give Part B compound (0.93 g, 60%) as a light yellow oil.

15

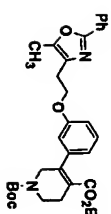
C.



Part B compound (0.594 g; 1.14 mmol) was converted to Part C Compound using the procedure described in Example 373 Part E. Part C compound was obtained as an oil, which was used in the next step without further purification. [M + H]<sup>+</sup> = 433.5

20

D.



25

To a solution of Part C compound in 1,4-dioxane/H<sub>2</sub>O (22 mL of a 1:1 v/v solution) was added di-tert-butyl dicarbonate (0.25 g, 1.137 mmol) and NaHCO<sub>3</sub> (0.24 g, 2.84 mmol). The mixture was stirred at RT for 2 h, then was partitioned between H<sub>2</sub>O (20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (15 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 15 mL). The

30

- 455 -

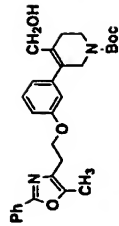


combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ),

concentrated in vacuo, and chromatographed ( $\text{SiO}_2$ ; 4:1 hex:EtOAc) to give Part D compound as a colorless oil (0.55 g, 91% yield over 2 steps).  $[\text{M} + \text{H}]^+ = 533.6$

5

E.

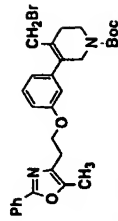


To a solution of Part D compound (0.55 g, 1.04 mmol) in THF (10 mL) at  $-78^\circ\text{C}$  was added  $\text{LiAlH}_4$  in THF (1.56 mL of a 1 M solution, 1.56 mmol). The reaction was

gradually warmed to  $10^\circ\text{C}$  and stirred for 12 h. Saturated aqueous  $\text{NH}_4\text{Cl}$  solution (10 mL) was added; precipitates were filtered off. The aqueous phase was extracted with

15  $\text{CH}_2\text{Cl}_2$  (3 X 10 mL). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), concentrated in vacuo and chromatographed ( $\text{SiO}_2$ ; 55:45 hex:EtOAc) to give Part E compound (0.389 g, 76%) as a white solid.  $[\text{M} + \text{H}]^+ = 491.6$

20 F.

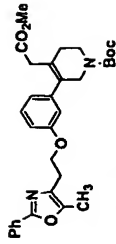


To a  $0^\circ\text{C}$  solution of Part E Compound (0.389 g, 0.792 mmol) and  $\text{PPh}_3$  (0.262 g, 0.991 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL) was

25 added  $\text{CBR}_4$  (0.332 g, 0.991 mmol) portionwise. The mixture was slowly warmed to RT and stirred at RT for 2 h. Volatiles were removed in vacuo, and the residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 90:10 to 85:15 hex:EtOAc) to afford Part F compound (0.407 g, 93%) as a light yellow oil.

30

G.



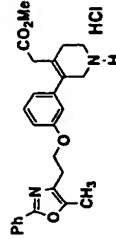
To a solution of Part F compound (0.371 g, 0.671 mmol) and  $(\text{PPh}_3)_2\text{Pd}$  (0.155 g, 0.134 mmol) in MeOH (8 mL) was added  $\text{KHCO}_3$  (0.268 g, 2.68 mmol). The mixture stirred at RT overnight under a pressure of 100 psi of CO gas in a stainless steel bomb. Volatiles were removed in vacuo and the residue was taken up in  $\text{H}_2\text{O}$  (10 mL) and

10 extracted with  $\text{CH}_2\text{Cl}_2$  (3 X 10 mL). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), concentrated in vacuo, and chromatographed (4:1 hex:EtOAc) to afford Part G compound (0.218 g, 61%) as a colorless oil.

$[\text{M} + \text{H}]^+ = 533.6$

15  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.91 (dd,  $J = 2.0$  &  $7.9$  Hz, 2 H), 7.33 (m, 3 H), 7.17 (s, 1 H), 7.16 (d,  $J = 10.6$  Hz, 1 H), 6.76 (d,  $J = 6.3$  Hz, 1 H), 6.68 (d,  $J = 6.3$  Hz, 1 H), 4.16 (t,  $J = 6.6$  Hz, 2 H), 3.96 (s, 2 H), 3.56 (s, 3 H), 3.50 (t,  $J = 5.5$  Hz, 2 H), 2.91 (m, 4 H), 2.30 (s, 3 H), 20 2.15 (br. s, 2 H), 1.39 (s, 9 H)

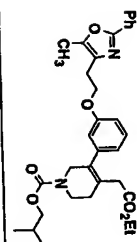
H.



25 Compound G (0.218 g; 0.410 mmol) was subjected to the acetyl chloride/MeOH deprotection conditions (as for Example 402 Part F compound) for the deprotection of the N-Boc group to give Part H compound as the HCl salt (0.171 g; 89%).  $[\text{M} + \text{H}]^+ = 433.5$

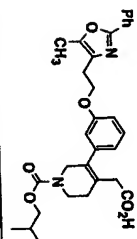
30

I



Part I compound was prepared from Part H compound and isobutyl chloroformate according to the procedure described for the synthesis of Example 363 Part B compound.

J.



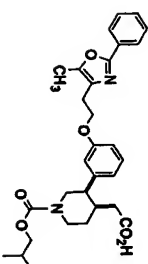
The title compound (white solid) was prepared from Part G compound by acid-mediated hydrolysis and purified by preparative HPLC according to the procedure described for the synthesis of Example 363.  $[M + H]^+ = 519.3$

Examples 407-408

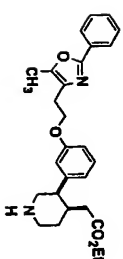
Examples 407-408 of the invention were prepared according to the procedures described for the synthesis of Example 406. The N-pyrimidine compound was synthesized using the procedure described for the synthesis of Example 364 Part B compound.

Example No	Structure	$[M + H]^+$
407		539.2
408		565.1

Example 409

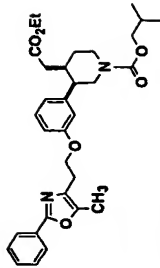


A.



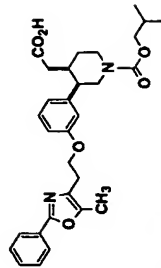
A mixture of Example 406 Part H compound (13.2 mg; 0.0282 mmol) and Pd/C (40 mg, 10%) in HOAc (10 mL) was stirred under an atmosphere of H<sub>2</sub> (60-70 psi) overnight to give Part A compound (12.2 mg; 100%).

B.



Part B compound was prepared from Part A compound and isobutyl chloroformate according to the procedure described for the synthesis of Example 363 Part B compound.

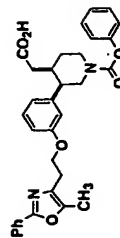
C.



The title compound (white solid) was prepared from Part B compound by acid-mediated hydrolysis and purified by preparative HPLC according to the procedure described for the synthesis of Example 363.

$[M + H]^+ = 521.1$

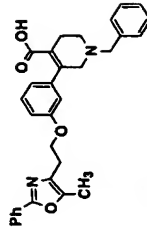
#### Example 410



Example 410 was prepared according to the general procedures described for the synthesis of Example 409.

$[M + H]^+ = 541.1$

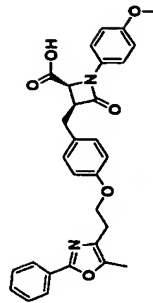
#### Example 413



The title compound was prepared from Example 406 Part B compound by acid-mediated hydrolysis according to the procedure described for the synthesis of Example 363. The crude product was purified by preparative HPLC (also according to the procedure of Example 363) to give the title compound (10.7 mg, 56.7%) as a white solid.

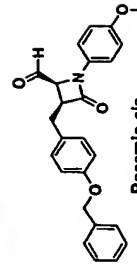
$[M + H]^+ = 495.5$

#### Example 414



Racemic cis

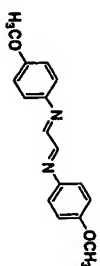
A.



Racemic cis

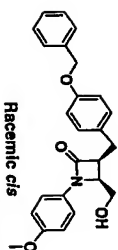
(Ref. Adlington, R.M. et al. *J. Med. Chem.* 2001, 44, 1491)

To a 45°C mixture of Example 419 Part A compound (3.0 g, 10.93 mmol)



and Et<sub>3</sub>N (1.6 mL, 11.5 mmol) in dry toluene (70 mL) under N<sub>2</sub> was added dropwise a solution of 3-(4-benzoyloxyphenyl)-propionyl chloride (prepared in the same manner as Example 419 Part E compound, but starting from 3-(4-hydroxyphenyl)propionic acid; 2.93 g in 5 mL toluene; 10.93 mmol) over 45 min. The solution was stirred at 45°C for another 4 h, cooled to RT and aqueous HCl (9 mL of concentrated HCl in 66 mL H<sub>2</sub>O) was added. The mixture was stirred at RT for 16 h, then extracted with EtOAc (200 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuo and the residue was chromatographed (SiO<sub>2</sub>; continuous gradient using hex:EtOAc from 100% hex to 100% EtOAc) to give Part A compound (1.71 g, 39%) as a yellow solid. [M - H]<sup>+</sup> = 400.1.

B.

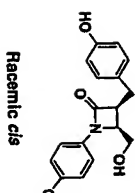


Racemic cis

A mixture of Part A compound (108 mg; 0.269 mmol) in THF (6 mL) and LiBH<sub>4</sub> (8 mg, 0.367 mmol) was stirred at RT overnight, then was partitioned between saturated aqueous NaHCO<sub>3</sub> and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 0 to 100% EtOAc-hexanes) to afford Part B compound as a white solid (60 mg, 55%). [M + H]<sup>+</sup> = 404.3.

C.

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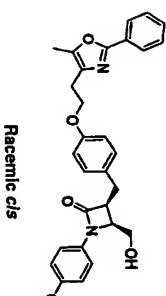


Racemic cis

A mixture of Part B compound (60 mg; 0.149 mmol) and 10% Pd/C (30 mg) in EtOAc (10 mL) was stirred under an atmosphere of H<sub>2</sub> (1 atm) at RT for 5 h. The catalyst was filtered off and the filtrate was concentrated in vacuo to give Part C compound (45 mg, 97%) as a colorless oil.

[M + Na]<sup>+</sup> = 336.2.

D.

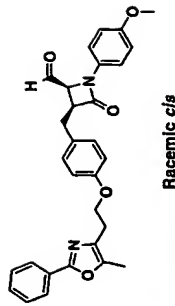


Racemic cis

A mixture of Part C compound (45 mg; 0.144 mmol), Example 23 Part A compound (62 mg; 0.22 mmol), and powdered K<sub>2</sub>CO<sub>3</sub> (45 mg; 0.33 mmol) in CH<sub>3</sub>CN (8 mL) was heated at reflux overnight, then cooled to RT and partitioned between EtOAc (25 mL) and H<sub>2</sub>O (25 mL). The organic phase was washed with water, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to give Part D compound (30 mg; 42%) as a colorless oil. [M + H]<sup>+</sup> = 499.4.

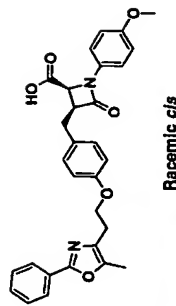
- 463 -

E.



To a dispersion of Dess-Martin periodinane (48 mg, 0.11 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was added dropwise a solution of Part D compound (30 mg, 0.06 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) and the resulting mixture was stirred at RT for 7 h. Volatiles were removed in vacuo and the residue was chromatographed ( $\text{SiO}_2$ ; continuous gradient from 100% hex to 100% EtOAc) to yield Part E compound (19.6 mg, 66%) as a pale yellow oil.  $[\text{M} - \text{H}]^+ = 495.3$ .

F.



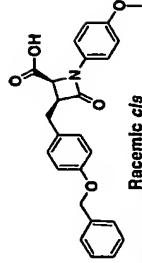
To a solution of Part E compound (19 mg, 0.04 mmol) in acetone (1.5 mL) was added Jones reagent (4 drops). The reaction was stirred at RT for 3 h and then partitioned between water and EtOAc (20 mL each). The organic phase was washed with  $\text{H}_2\text{O}$ , brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; flow rate = 20 mL/min; 10 min continuous gradient from 70:30 B:A to 100% B, where solvent A = 90:10:0.1  $\text{H}_2\text{O}$ :MeOH:TFA and solvent B = 90:10:0.1 MeOH: $\text{H}_2\text{O}$ :TFA) to give the title compound (4.9 mg; 25%).  $[\text{M} + \text{H}]^+ = 513.3$ .

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$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.38 (s, 3H), 2.87 (dd, J = 14.9, 7.47 Hz, 1H), 2.95-3.1 (m, 3H), 3.75 (s, 3H), 3.7-3.8 (m, 1H), 4.05-4.15 (br. t, J = 6.15 Hz, 2H), 4.58 (d, J = 5.72 Hz, 1H), 6.69 (d, J = 8.36 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.36 Hz, 2H), 7.27 (d, J = 9.24 Hz, 2H), 7.35-7.45 (m, 3H), 7.92 (d, J = 7.48 Hz, 2H).

# Alternative sequence: Example 414

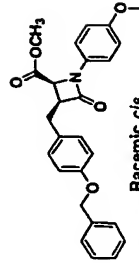
10 G.



To a solution of Example 414 Part A compound (979 mg, 2.44 mmol) in acetone (75 mL) was added Jones reagent (2.6 mL) dropwise. The reaction was stirred at RT for 0 °C for 1.5 h, concentrated in vacuo. The residue was partitioned between water and EtOAc (100 mL each). The organic phase was washed with  $\text{H}_2\text{O}$ , brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give the crude Part G compound (787 mg) which was used in the next step without further purification.

$[\text{M} + \text{H}]^+ = 418.5$ .

H.



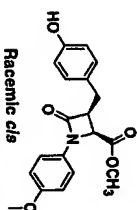
25

To a 0°C solution of the crude Part G compound in  $\text{CH}_2\text{Cl}_2$ : $\text{CH}_3\text{OH}$  (1:1, 20 mL) was added TMSCHN<sub>3</sub> (3 mL of a 2M solution in hexanes, 6 mmol) dropwise and the mixture was stirred at 0°C for 1 h. Volatiles were removed in vacuo and the residue was chromatographed ( $\text{SiO}_2$ ; continuous

- 465 -

gradient from 100% hex to 100% EtOAc) to give Part H compound (477 mg, 45% for 2 steps) as an off-white solid.  $[M + H]^+ = 432.5$ .

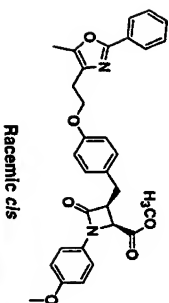
I.



A mixture of Part H compound (76 mg; 0.176 mmol)

and 10% Pd/C (33 mg) in EtOAc (5 mL) was stirred overnight under an atmosphere of  $H_2$  (1 atm) at RT. HPLC indicated incomplete conversion. More 10% Pd/C (37 mg) was added and the mixture was stirred for a further 2 h under  $H_2$ . The catalyst was filtered off and the filtrate was concentrated in vacuo to give Part I compound (49 mg, 81%) as a white solid.

J.

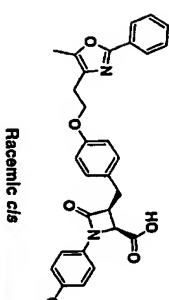


A mixture of Part I compound (49 mg; 0.144 mmol),

Example 23 Part A compound (65 mg; 0.23 mmol) and powdered  $K_2CO_3$  (40 mg; 0.29 mmol) in  $CH_3CN$  (10 mL) was heated under reflux overnight, at which point HPLC indicated incomplete conversion. More Example 23 Part A compound (63 mg; 0.22 mmol) and  $K_2CO_3$  (49 mg; 0.36 mmol) were added and the mixture heated at reflux for a further 12 h, then was cooled to RT and partitioned between EtOAc and  $H_2O$  (25 mL each). The aqueous phase was extracted with EtOAc (x 2) and the combined organic extracts were washed with water, brine, dried ( $Na_2SO_4$ ) and concentrated

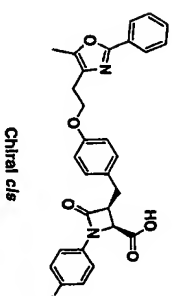
in vacuo. The residue was chromatographed ( $SiO_2$ ; continuous gradient from 100% hexane to 100% EtOAc) to give Part J compound (68 mg; 83%) as a colorless oil.  $[M + H]^+ = 526.8$ .

K.



A solution of Part H compound (67 mg, 0.127 mmol) and  $LiOH \cdot H_2O$  (10 mg, 0.238 mmol) in  $H_2O$  (0.3 mL) in THF (1.2 mL) was stirred for 5 h at RT, then was partitioned between EtOAc (20 mL) and aqueous 1N HCl (10 mL). The aqueous phase was extracted with EtOAc (x 2) and the combined organic extracts were washed with brine, dried ( $Na_2SO_4$ ), and evaporated in vacuo to yield the title compound (60.5 mg; 93%) as a white solid.  $[M + H]^+ = 513.4$ .

#### Example 415



The racemic Example 414 Part J compound (31 mg) was separated into the two individual enantiomers by preparative HPLC (Chiracel chiral AD 5 x 50 cm column; flow rate = 45 mL/min; isocratic mobile phase 65:35 A:B, where solvent A = heptane + 0.1% TFA and solvent B =

isopropanol + 0.1% TFA). The faster eluting fraction was concentrated in vacuo to give Example 415.

$[M + H]^+ = 513.4$ ;  $[\alpha]_D = -16.0^\circ$  ( $c = 0.075$ ,  $CDCl_3$ ,  $24^\circ C$ );

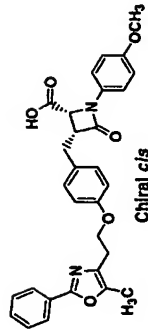
The absolute stereochemistry is arbitrarily assigned. The  $^1H$  NMR spectrum is identical to Example 414.

Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column, flow rate = 1 mL/min; isocratic conditions =

65:35 A:B, where A = heptane + 0.1% TFA and B = IPA +

0.1% TFA; detector wavelength = 264 nm): retention time = 9.91 min; ee = 96%.

#### Example 416



15

The slower eluting fraction in the above

separation was evaporated in vacuo to give Example 416.

$[M + H]^+ = 513.4$ ;  $[\alpha]_D = +20.77^\circ$  ( $c = 0.062$ ,  $CDCl_3$ ,  $24^\circ C$ );

Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column, flow rate = 1 mL/min; isocratic conditions =

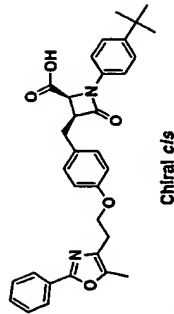
65:35 A:B, where A = heptane + 0.1% TFA and B = IPA +

0.1% TFA; detector wavelength = 264 nm): retention time = 15.96 min; ee = >99%. Absolute stereochemistry is

arbitrarily assigned.  $^1H$  NMR: identical to Example 414.

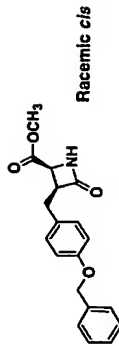
25

#### Example 417



30

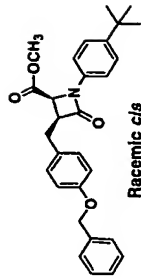
A.



To a 0  $^\circ C$  solution of Example 414 Part H compound (366 mg; 0.85 mmol) in  $CH_3CN$  (15 mL) was added aqueous ammonium cerium nitrate (990 mg; 1.8 mmol in 5 mL  $H_2O$ ). The reaction mixture was stirred at 0  $^\circ C$  for 3 h, then EtOAc (100 mL) was added. The organic phase was washed

with saturated aqueous  $Na_2SO_3$  (15 mL), dried ( $Na_2SO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; continuous gradient from 100% hex to 100% EtOAc) to give Part A compound (173 mg; 63%) as a yellow solid.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  2.81 (dd,  $J = 15.4$ , 8.4 Hz, 1H), 3.00 (dd,  $J = 14.9$ , 7.9 Hz, 1H), 3.62 (s, 3H), 3.83 (br. q,  $J = 7.92$  Hz, 1H), 4.28 (d,  $J = 5.72$  Hz, 1H), 4.98 (s, 2H), 6.14 (br. s, 1H), 6.89 (d,  $J = 8.32$  Hz, 2H), 7.12 (d,  $J = 8.36$  Hz, 2H), 7.26-7.43 (m, 5H);  $[M - H]^+ = 324.6$

B.



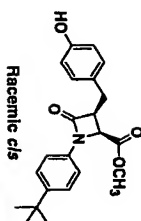
20

To a solution of the Part A compound (57.7 mg, 0.178 mmol) in DCE (2.5 mL) was added p-t-butyl phenylboronic acid (66 mg, 0.37 mmol),  $Cu(OAc)_2$  (34 mg 0.187),  $Et_3N$  (74  $\mu L$ , 0.53 mmol), pyridine (55  $\mu L$ , 0.68 mmol) and 4A molecular sieves (33 mg; pre-dried at 400 $^\circ C$  overnight). Air was allowed to pass into the reaction mixture, which was stirred at RT for 1.5 h. The volatiles were removed

in vacuo and the residue was chromatographed ( $SiO_2$ ;

continuous gradient from 100% hex to 100% EtOAc) to give Part B compound (49 mg, 60%) as a colorless oil.  
[M + H]<sup>+</sup> = 458.5.

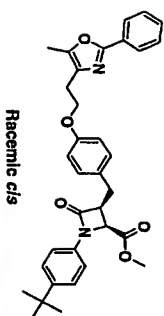
5 C.



10 A mixture of Part B compound and 10% Pd/C (49 mg) in EtOAc (5 mL) was stirred under an atmosphere of H<sub>2</sub> (1 atm) at RT for 2 h. The catalyst was filtered off and the filtrate was concentrated in vacuo to give Part C compound, which was used in the next step without further purification.

15 [M + H]<sup>+</sup> = 368.4.

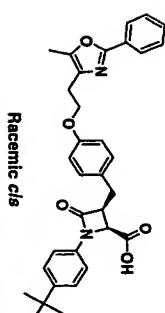
D.



20 A mixture of crude Part C compound, Example 23

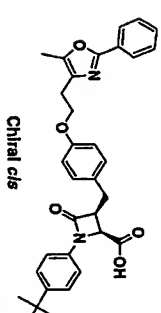
Part A compound (65 mg; 0.23 mmol) and powdered K<sub>2</sub>CO<sub>3</sub> (70 mg; 0.51 mmol) in CH<sub>3</sub>CN (3 mL) was stirred at 95°C for 16 h, then cooled to RT and partitioned between EtOAc (20 mL) and aqueous 1N HCl (10 mL). The aqueous layer was extracted with EtOAc (x 2) and the combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 100% EtOAc) to afford Part D compound (50.3 mg, 85%) as a colorless oil.

E.



5 A solution of Part D compound (50 mg, 0.091 mmol) and LiOH·H<sub>2</sub>O (9 mg, 0.214 mmol) in H<sub>2</sub>O (0.5 mL) and THF (3 mL) was stirred for 7 h at RT, then partitioned between EtOAc (20 mL) and aqueous 1N HCl (10 mL). The aqueous layer was extracted with EtOAc (x 2) and the combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; flow rate = 20 mL/min; 10 min continuous gradient from 60:40 B:A to 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give Part E compound.

F.



20

25 Part E compound was separated into the two individual enantiomers by preparative HPLC (Chiracel chiral AD 5 X 50 cm column; flow rate = 45 mL/min; isocratic mobile phase 85:15 A:B, where solvent A = Heptane + 0.1% TFA and solvent B = IPA + 0.1% TFA). The faster eluting fraction was evaporated in vacuo to give Example 417 (15 mg, 31% yield; 50% of theoretical recovery).



$[M + H]^+ = 539.4$ .

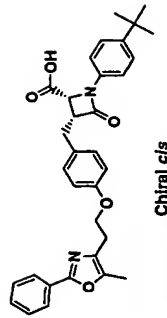
Absolute stereochemistry is tentatively assigned.

$^1H$  NMR:  $\delta$  1.21 (s, 9H), 2.33 (m, 3H), 2.82 (dd,  $J = 14.94$ , 7.9 Hz, 1H), 2.92-3.05 (m, 3H), 3.72 (q,  $J = 7.48$  Hz, 1H), 3.95-4.1 (m, 2H), 4.54 (d,  $J = 6.16$  Hz, 1H), 6.64 (d,  $J = 8.36$  Hz, 2H), 6.96 (d,  $J = 8.36$  Hz, 2H), 7.18-7.4 (m, 7H), 7.86 (d,  $J = 7.48$  Hz, 2H), 9.98 (br. s, 1H).

Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column, flow rate = 1 mL/min; isocratic conditions = 60:40 A:B, where A = heptane + 0.1% TFA and B = IPA + 0.1% TFA; detector wavelength = 254 nm): retention time = 10.96 min; ee = 99%, Purity = 85% (contained 15% trans-isomer).

15

#### Example 418



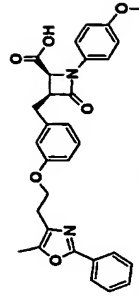
The slower eluting fraction in the above separation was evaporated in vacuo to give Example 418 (8 mg, 16% yield; 50% of theoretical recovery).

$[M + H]^+ = 539.4$

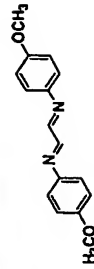
Absolute stereochemistry is arbitrarily assigned.  $^1H$  NMR: Identical to Example 417.

Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column, flow rate = 1 mL/min; isocratic conditions = 60:40 A:B, where A = heptane + 0.1% TFA and B = IPA + 0.1% TFA; detector wavelength = 254 nm): retention time = 21.84 min; ee = 99%, Purity = 99%.

#### Example 419

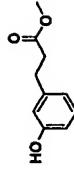


5 A.



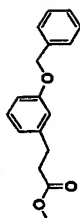
To a solution of p-anisidine (12.3 g; 0.1 mol) in MeOH (60 mL) at 58°C was added glyoxal (13.4 g, 40% solution in H<sub>2</sub>O, 0.05 mol) over 2 min. The reaction mixture was stirred at 58°C for another 2 min, then cooled to RT. The mixture was filtered to give Part A compound as a yellow solid (11.0 g, 82%).

15 B.



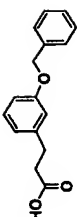
To a solution of 3-(3-hydroxyphenyl)propionic acid (18.5 g, 0.11 mol) in MeOH (150 mL) at RT was added concentrated H<sub>2</sub>SO<sub>4</sub> (3 mL). The reaction mixture was stirred at 50°C for 1 h. Volatiles were removed in vacuo and the residue was partitioned between saturated aqueous NaHCO<sub>3</sub> (70 mL) and EtOAc (400 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give crude Part B compound (20.0 g, 99%) as an oil.

C.



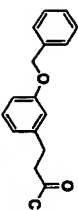
A mixture of Part B compound (20.0 g, 0.11 mol), benzyl bromide (13.5 mL, 0.113 mol) and powdered  $K_2CO_3$  (22.7 g, 0.164 mol) in  $CH_3CN$  (400 mL) was stirred at 70°C for 12 h, then cooled to RT and filtered. The filtrate was concentrated in vacuo to give Part C compound (30.0 g; 100%) as an oil.

10 D.



A solution of Part C compound (30 g, 0.111 mol) and aqueous LiOH (5.57 g in 300 mL  $H_2O$ , 0.132 mol) in THF (300 mL) was stirred at RT for 16 h, after which more LiOH ( $H_2O$  (1.0 g, 0.238 mmol) was added. The reaction was stirred at RT for another 36 h, then acidified to pH 4 with concentrated HCl. Organic volatiles were removed in vacuo and the aqueous phase was extracted with EtOAc (2 X 100 mL). The combined organic extracts were dried ( $MgSO_4$ ) and concentrated in vacuo to give Part D compound (28.1 g, 99%).

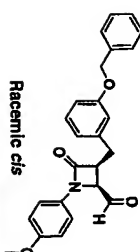
E.



To a 0°C solution of Part D compound (28.1 g, 0.111 mol) in  $CH_2Cl_2$  (100 mL) were added DMF (0.5 mL) and oxalyl chloride (20 mL, 0.229 mol) over 75 min. The reaction was stirred at RT for 1 h. Volatiles were removed in

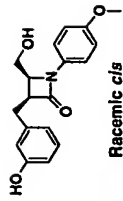
vacuo and the residue was distilled (Kugelrohr; bp = 200°C @ 0.1 mm Hg) to give Part E compound (24.2 g; 80%) as a clear oil.

5 F.



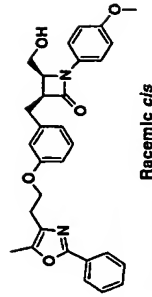
Ref: Adlington, R.M. et al J. Med. Chem. 2001, 44, 1491  
To a mixture of Part A compound (3.8 g, 0.014 mol) and  $Et_3N$  (3.39 mL, 0.024 mol) in dry toluene (110 mL) at 40°C under  $N_2$  was added dropwise a solution of Part E compound (6.77 g in 5 mL toluene; 0.0247 mol) over 2.5 h. The reaction was stirred at 35-40°C for another 1.5 h, then cooled to RT and aqueous HCl (20 mL of conc. HCl in 130 mL  $H_2O$ ) was added. The mixture was stirred at RT for 16 h and extracted with EtOAc (250 mL). The combined organic extracts were dried ( $Na_2SO_4$ ), concentrated in vacuo, and the residue was recrystallized from  $Et_2O$  to give Part F compound. In addition, the combined mother liquors were concentrated in vacuo, and the residue was chromatographed ( $SiO_2$ ; continuous gradient from 100% hex to 55:45 hex:EtOAc over 35 min, 55:45 hex:EtOAc for 10 min) to give additional Part F compound (combined recovery = 4.03 g, 80%) as a solid.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  2.87 (dd, J = 14.4, 9.7 Hz, 1H), 3.30 (dd, J = 9.7, 6.2 Hz, 1H), 3.77 (s, 3H), 4.02 (dt, J = 9.7, 6.2 Hz, 1H), 4.56 (dd, J = 6.2, 2.7 Hz, 1H), 5.05 (s, 2H), 6.86-7.50 (m, 13H), 9.60 (d, J = 2.7 Hz, 1H);  $[M + H]^+ = 402.3$ .

G.



- 5 A mixture of Part F compound (2.0 g, 4.98 mmol) and 10% Pd/C (1.85 g) in EtOAc (150 mL) was stirred under an atmosphere of H<sub>2</sub> (60 psi) at RT for 24 h, at which point the reaction was complete by HPLC. The catalyst was filtered off (Celite®) and the filtrate was concentrated in vacuo to give Part G compound (1.42 g, 91%) as a white foam.
- 10

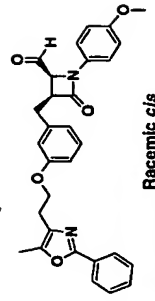
H.



- 15 A mixture of Part G compound (1.42 g; 4.53 mmol), Example 23 Part A compound (1.91 g; 6.79 mmol) and powdered K<sub>2</sub>CO<sub>3</sub> (1.37 g; 9.93 mmol) in CH<sub>3</sub>CN (40 mL) was stirred at 85°C for 22 h. At this point analytical HPLC indicated that all starting material had been consumed. The reaction mixture was partitioned between Et<sub>2</sub>O (200 mL) and H<sub>2</sub>O (50 mL). The organic phase was washed with water (2 x 50 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from 5:1 to 2:1 hex:EtOAc) to give Part H compound (1.36 g; 60%) as a white foam.
- 20
- 25

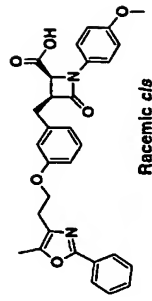
- 476 -

I.



- 5 To a mixture of Dess-Martin periodinane (116 mg; 0.27 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL) at RT was added a solution of Part H compound (100 mg; 0.20 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL). The reaction was stirred at RT for 30 min. Volatiles were removed in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 2:1 hex:EtOAc) to give Part I compound (96 mg; 96%) as an oil.
- 10

J.



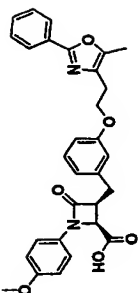
- 15 To a 0°C solution of Part I compound (96 mg, 2.23 mmol) in acetone (75 mL) was added Jones reagent (2.25 mL) dropwise. The reaction was stirred at RT for 30 min, after which volatiles were removed in vacuo and the residue was partitioned between water (60 mL) and EtOAc (200 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give the crude product, which was filtered through SiO<sub>2</sub> (100% EtOAc). Volatiles were removed in vacuo and the residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; flow rate = 20 mL/min; 10 min hold-time gradient from 70:30 B:A to 100% B + 10 min hold-time at 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B =
- 20
- 25

- 477 -

90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give Example 419 (32 mg; 32%).  
 $[M + H]^+ = 513.4$

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.40 (s, 3H), 2.99 (t,  $J = 8.7$  Hz, 2H), 3.23 (dd,  $J = 14.5, 12.3$  Hz, 1H), 3.32 (dd,  $J = 14.5, 3.5$  Hz, 1H), 3.78 (s, 3H), 3.83-3.92 (m, 1H), 4.20-4.45 (m, 2H), 4.50 (d,  $J = 5.7$  Hz, 1H), 6.80-6.98 (m, 5H), 7.20-7.50 (m, 6H), 7.92-7.98 (m, 2H).

#### Example 420

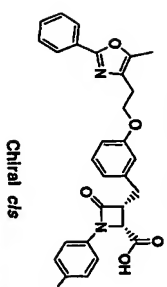


Chiral *cis*

The individual enantiomers of Example 419, Part J compound were separated by preparative HPLC (Chiralcel chiral OD 5 X 50 cm column; flow rate = 45 mL/min; isocratic mobile phase 70:30 A:B, where solvent A =

Heptane + 0.1% TFA and solvent B = isopropanol + 0.1% TFA). The faster eluting fraction yielded Example 420.  $[M + H]^+ = 513.2$ ;  $[\alpha]_D = -74.8^\circ$  ( $c = 0.16$ , CDCl<sub>3</sub>, 25°C); Absolute stereochemistry is tentatively assigned. <sup>1</sup>H NMR: Identical to Example 419. Chiral analytical HPLC (Daicel Chiralcel AD 4.6 X 250 mm column): flow rate = 1 mL/min; isocratic conditions = 70:30 A:B, where A = heptane + 0.1% TFA and B = isopropanol + 0.1% TFA; detector wavelength = 264 nm; retention time = 7.89 min; ee > 99%.

#### Example 421

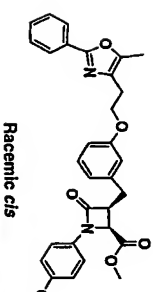


Chiral *cis*

The slower eluting fraction from the above chiral separation (Example 420) yielded Example 421. (The isocratic mobile phase changed to 60:40 A:B after the faster eluting enantiomer came out, where solvent A = Heptane + 0.1% TFA and solvent B = IPA + 0.1% TFA);  $[M + H]^+ = 513.4$ ;  $[\alpha]_D = +58.8^\circ$  ( $c = 0.16$ , CDCl<sub>3</sub>, 25°C); Absolute stereochemistry is tentatively assigned. <sup>1</sup>H NMR: identical to Example 419.

An alternative method was developed for preparation of Examples 420 and 421.

A.

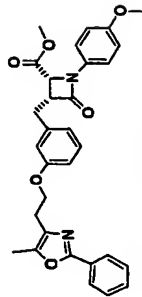


Racemic *cis*

To a 0°C solution of Example 419, part J compound (800 mg, 1.56 mmol) in CH<sub>2</sub>Cl<sub>2</sub>/MeOH (8.3 mL/8.3 mL) was added a solution of TMSCHN<sub>3</sub> (3.7 mL of a 2M solution in hexane; 0.074 mmol). The mixture was stirred at RT for 30 min. Volatiles were removed in vacuo and the residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 60:40 hex:EtOAc over 30 min, 60:40 hex:EtOAc for

10 min) to give Part A compound (0.4 g, 49%).  $[M + H]^+ = 527.2$ .

B.



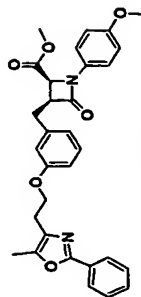
Chiral cis

5

The two enantiomers of the racemate (Part A compound) were separated by preparative HPLC (Chiralcel Chiral OD 5 x 50 cm column; flow rate = 45 mL/min; isocratic mobile phase 60:40 A:B, where solvent A = Heptane + 0.1% TFA and solvent B = IPA + 0.1% TFA). The faster eluting fraction yielded Part B compound and slowing eluting enantiomer afforded Part C compound below

15 (the isocratic mobile phase changed to 20:80 A:B after fractions containing faster eluting enantiomer were collected, where solvent A = Heptane + 0.1% TFA and solvent B = IPA + 0.1% TFA). Chiral analytical HPLC (Daicel Chiralcel OD 4.6 x 250 mm column): flow rate = 1.5 mL/min; isocratic conditions = 60:40 A:B, where A = heptane and B = IPA, detector wavelength = 264 nm; retention time = 32.9 min;

C.



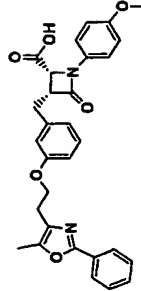
Chiral cis

25

Chiral analytical HPLC (Daicel Chiralcel OD 4.6 x 250 mm column): flow rate = 1.5 mL/min; isocratic

conditions = 60:40 A:B, where A = heptane and B = IPA, detector wavelength = 264 nm; retention time = 42.7 min;

D.



Chiral cis

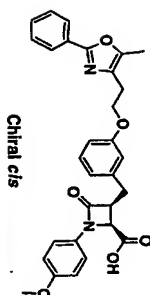
5

To a solution of Part B compound (146 mg, 0.277 mmol) in THF (6 mL) was added a solution of aqueous LiOH (23.3 mg in 3 mL H<sub>2</sub>O, 0.554 mmol). The reaction mixture was stirred at RT for 16 h after which it was acidified to pH 3 with excess aqueous 1 M HCl, then organic solvents were removed in vacuo. The residual aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic extracts were successively washed with H<sub>2</sub>O and brine (50 mL each); dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo to give Example 421 compound as a white solid (120 mg; 85%).  $[M + H]^+ = 513.2$ ;  $[\alpha]_D = +83.1^\circ$  (c = 0.16, CHCl<sub>3</sub>, 25°C).

<sup>1</sup>H NMR: identical to Example 419.

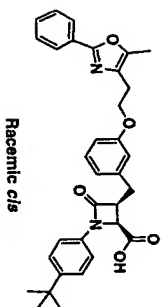
Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 70:30 A:B, where A = heptane + 0.1% TFA and B = IPA+0.1% TFA; detector wavelength = 264 nm; retention time = 12.9 min; ee > 93%

E.

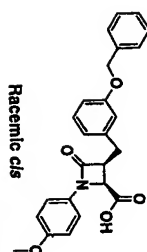


- 5 A solution of Part C compound (90 mg, 0.171 mmol) in THF (4 mL) and aqueous LiOH (14.3 mg in 1.8 mL H<sub>2</sub>O, 0.34 mmol) was stirred at RT for 16 h, then was acidified to pH 3 with excess aqueous 1 M HCl. The organic volatiles were removed in vacuo. The residual aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic extracts were successively washed with H<sub>2</sub>O and brine (50 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give Example 420 compound as a white solid (70 mg; 80%); [M + H]<sup>+</sup> = 513.2; [α]<sub>D</sub> = - 82.3° (c = 0.18, CDCl<sub>3</sub>, 25°C).
- 15 <sup>1</sup>H NMR: identical to Example 419.

- 20 Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 70:30 A:B, where A = heptane + 0.1% TFA and B = IPA+0.1% TFA; detector wavelength = 264 nm; retention time = 8.0 min; ee > 99%

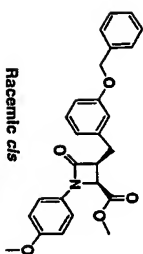
Example 422

A.



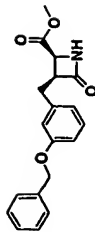
- 5 To a 0°C solution of Example 419, Part F compound (0.896 g, 2.23 mmol) in acetone (75 mL) was added Jones reagent (2.25 mL) dropwise. The reaction mixture was stirred at RT for 30 min. Volatiles were removed in vacuo and the residue was partitioned between water (60 mL) and EtOAc (200 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part A compound which was used in the next step without further purification.
- 15 [M + H]<sup>+</sup> = 418.3.

B.



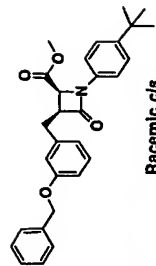
- 20 To a 0°C solution of Part A compound in CH<sub>2</sub>Cl<sub>2</sub>/MeOH (7 mL/7 mL) was added TMSCl, in hexane (3 mL of a 2M solution). The reaction was stirred at RT for 30 min. Volatiles were removed in vacuo and the residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 50:50 hex:EtOAc over 30 min) to give Part B compound (0.60 g, 62%). [M + H]<sup>+</sup> = 432.4.

C.

Racemic *cis*

- 5 To a 0°C solution of Part B compound (0.60 g; 1.4 mmol) in CH<sub>3</sub>CN (17 mL) was added a solution of ceric ammonium nitrate (1.5 g; 2.73 mmol) in H<sub>2</sub>O (9.6 mL). The reaction mixture was stirred at 0°C for 20 min, then EtOAc (150 mL) was added. The organic phase was washed with saturated aqueous sodium sulfite (15 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from 3:1 to 1:1 hex:EtOAc) to give Part C compound (0.342 g; 75%) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.78 (dd, J = 14.9, 8.4 Hz, 1H), 3.01 (dd, J = 14.9, 7.5 Hz, 1H), 3.57 (s, 3H), 3.81 (m, 1H), 4.24 (d, J = 5.7 Hz, 1H), 4.98 (bs, 1H), 5.03 (s, 2H), 6.70-6.85 (m, 3H), 7.13 (t, J = 7.9 Hz, 1H), 7.25-7.40 (m, 5H); [M + H]<sup>+</sup> = 326.3.

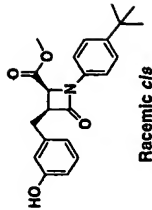
20 D.

Racemic *cis*

- To a solution of the Part C compound (27.9 mg, 0.086 mmol) in DCE (1.2 mL) was added p-tert-butyl phenylboronic acid (31.3 mg, 0.176 mmol), Cu(OAc)<sub>2</sub> (16 mg, 0.088 mmol), Et<sub>3</sub>N (35 μL, 0.25 mmol), pyridine (25 μL, 0.31 mmol) and 4 Å molecular sieves (150 mg; pre-dried at

400°C overnight). Air was allowed to pass into the reaction mixture, which was stirred at RT for 1.5 h. Volatiles were removed in vacuo and the residue was chromatographed (SiO<sub>2</sub>; 3:1 hex:EtOAc) to give Part D compound (38.6 mg, 98%). [M + H]<sup>+</sup> = 458.3.

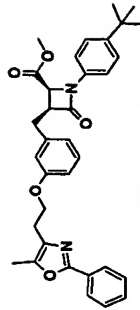
E.

Racemic *cis*

- 10 A mixture of Part D compound (38.6 mg; 0.084 mmol) and 10% Pd/C (20 mg) in EtOAc (3 mL) was stirred under an atmosphere of H<sub>2</sub> (balloon) at RT for 3 h, at which point the reaction was complete by HPLC. The catalyst was filtered off (Celite®) and the filtrate was concentrated in vacuo to give Part E compound (20 mg, 65%) as a solid. [M + H]<sup>+</sup> = 367.3.

15

F.

Racemic *cis*

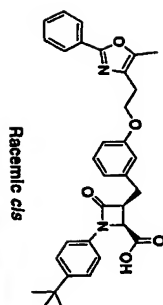
20

- A mixture of Part E compound (13.2 mg; 0.036 mmol), Example 23 Part A compound (30 mg; 0.107 mmol) and powdered K<sub>2</sub>CO<sub>3</sub> (23 mg; 0.167 mmol) in CH<sub>3</sub>CN (1.5 mL) was stirred at 85°C for 16 h, after which precipitates were filtered. The filtrate was concentrated in vacuo and the residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from

25

3:1 to 1.5:1 hex:EtOAc) to give Part F compound (11.1 mg; 56%) as an oil.  $[M + H]^+ = 553.4$ .

G.



5

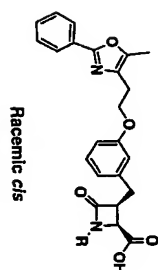
A solution of Part F compound (11.1 mg, 0.019 mmol) and aqueous LiOH.H<sub>2</sub>O (2 mg in 0.6 mL H<sub>2</sub>O, 0.047 mmol) in THF (0.8 mL) was stirred at RT for 16 h, after which more LiOH.H<sub>2</sub>O (2 mg, 0.047 mmol) was added. After stirring for another 24 h, the mixture was acidified to pH 4 with 1 M aqueous HCl. Volatiles were removed in vacuo and the residue was partitioned between water (2 mL) and EtOAc (6 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (continuous gradient over 12 min from 75:25 A:B to 100%B; A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA; B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA; flow rate = 20 mL/min; detection at 220 nm; YMC ODS 20 x 100 mm column) to give Example 422 (2.08 mg; 19%) as a viscous oil.  $[M + H]^+ = 539.2$ .

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### Examples 423-427

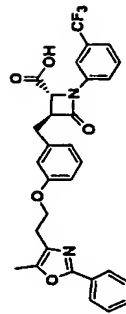
Examples 423-427 were prepared in the same fashion as Example 422 (from Example 422, Part C compound) using the appropriately substituted phenyl boronic acids.

5



Example #	R	$[M + H]^+$
423		501.2
424		517.1
425		575.2
426		514.2
427		551.1



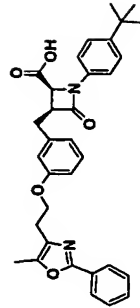
Example 428*Racemic trans*

5 During the preparation of Example 427, at the final hydrolysis step, a slower eluting side product was isolated by preparative HPLC and was determined to be the corresponding trans diastereomer (title compound). The epimerization was presumed to have occurred at the

10 carboxylic acid stereocenter.

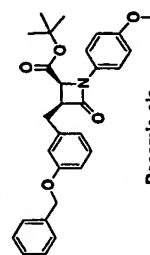
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.24 (s, 3H), 2.86 (t, J = 6.6 Hz, 2H), 3.00-3.15 (m, 2H), 3.60-3.63 (m, 1H), 4.15 (t, J = 6.6 Hz, 2H), 4.36 (s, 1H), 6.68-6.85 (m, 3H), 7.10 (t, J = 7.7 Hz, 1H), 7.25-7.50 (m, 6H), 7.55 (s, 1H), 7.85-7.90 (m, 2H); [M + H]<sup>+</sup> = 551.3.

15

Example 429*Chiral cis*

20

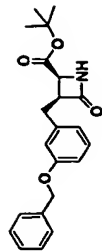
A.

*Racemic cis*

To a 0°C solution of Example 422, Part A compound (2.3 g, 5.73 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (9 mL) was added a solution of t-butyl 2,2,2-trichloroacetimidate (3.55 mL, 19.8 mmol) and BF<sub>3</sub>·OEt<sub>2</sub> (0.305 mL, 2.4 mmol). The mixture was stirred at RT for 2h, after which excess solid NaHCO<sub>3</sub> was added and stirring was continued for 5 min. Solids were filtered off (Celite®) and the filtrate was concentrated in vacuo to give a residue which was chromatographed (SiO<sub>2</sub>; continuous gradient from 100% hex to 75:25 hex:EtOAc over 25 min, hold at 75:25 hex:EtOAc for 15 min) to give Part A compound (1.66 g, 62 %). [M + H]<sup>+</sup> = 474.5

5 10 15

B.

*Racemic cis*

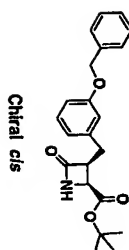
To a 0°C solution of Part A compound (1.78 g; 1.64 mmol) in CH<sub>3</sub>CN (50 mL) was added aqueous ceric ammonium nitrate solution (4.12 g; 7.51 mmol in 28 mL of H<sub>2</sub>O).

20

The reaction mixture was stirred at 0°C for 20 min, then was partitioned between EtOAc (250 mL) and saturated aqueous sodium sulfite (50 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from 3:1 to 2:1 hex:EtOAc) to give Part B compound (1.13 g; 82%) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.40 (s, 9H), 2.93 (dd, J = 15.4, 7.9 Hz, 1H), 3.06 (dd, J = 14.9, 7.9 Hz, 1H), 3.83 (m, 1H), 4.24 (d, J = 5.7 Hz, 1H), 5.01 (s, 2H), 6.02 (bs, 1H), 6.84 (dd, J = 8.4, 2.2 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 6.93 (s, 1H), 7.21 (t, J = 7.9 Hz, 1H), 7.30-7.45 (m, 5H); [M + Na]<sup>+</sup> = 390.2.

25 30

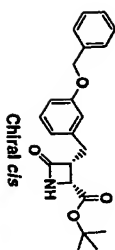
C.



The two enantiomers of racemic Part B compound were separated preparative HPLC (Chiralcel chiral AD 5 X 50 cm column; flow rate = 45 mL/min; isocratic mobile phase 92:8 A:B for 60 min, 85:15 A:B for 60 min, 80:20 A:B for 60 min, 77:23 A:B for 60 min, where solvent A = Heptane + 0.1% TFA and solvent B = isopropanol + 0.1% TFA). The faster eluting fraction was designated as Part C compound.  $[M + Na]^+ = 390.2$ ;  $[\alpha]_D = +23.5^\circ$  ( $c = 0.41$ ,  $CDCl_3$ ,  $25^\circ C$ ).

Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 70:30 A:B, where A = heptane + 0.1% TFA and B = IPA+0.1% TFA; detector wavelength = 254 nm; retention time = 9.43 min; ee > 99%

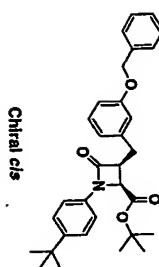
20 D.



The slower eluting fraction was designated as Part D compound.  $[M + Na]^+ = 390.2$ ;  $[\alpha]_D = -17.9^\circ$  ( $c = 0.45$ ,  $CDCl_3$ ,  $25^\circ C$ ). Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 70:30 A:B, where A = heptane + 0.1% TFA and B = IPA+0.1% TFA; detector wavelength = 254 nm; retention time = 29.1 min; ee > 97.5%

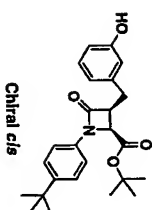
- 490 -

E.



To a solution of Part C compound (270 mg, 0.75 mmol) in DCE (12 mL) was added p-tert-butyl phenylboronic acid (377 mg, 2.11 mmol),  $Cu(OAc)_2$  (160 mg, 0.88 mmol),  $Et_3N$  (0.511 mL, 3.67 mmol), pyridine (297  $\mu L$ , 3.67 mmol) and 4A molecular sieves (200 mg; pre-dried at  $400^\circ C$  overnight). Air was allowed to pass into the reaction mixture, which was stirred at RT for 5 h. The solid was filtered off (Celite®) and the filtrate was concentrated in vacuo to give a residue which was chromatographed ( $SiO_2$ ; continuous gradient from 10% hex to 75:25 hex:EtOAc over 25 min, hold at 75:25 hex:EtOAc for 15 min) to give Part E compound (355 mg, 96%).  $[M + H]^+ = 500.3$ .

F.

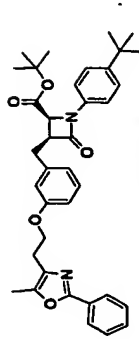


A mixture of Part E compound (355 mg; 0.71 mmol) and 10% Pd/C (200 mg) in EtOAc (40 mL) was stirred under an atmosphere of  $H_2$  (balloon) at RT for 3 h, at which point the reaction was complete by HPLC. The catalyst was filtered off (Celite®) and the filtrate was concentrated in vacuo to give a residue which was chromatographed ( $SiO_2$ ; stepwise gradient from 4:1 to 3:1

- 491 -

hex:EtOAc to 1:1 hex:EtOAc) to give Part F compound as a white solid (254 mg, 87%).  $[M + H]^+ = 410.4$ .

G.

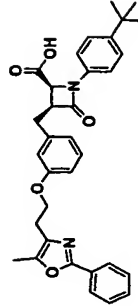


Chiral cis

A mixture of Part F compound (200 mg; 0.49 mmol), Example 23 Part A compound (302 mg; 1.07 mmol) and

- 10 powdered  $K_2CO_3$  (270 mg; 1.96 mmol) in  $CH_3CN$  (15 mL) was stirred at  $85^\circ C$  for 22h, then was cooled to RT and the precipitates were filtered off. The filtrate was concentrated in vacuo and the residue was chromatographed ( $SiO_2$ ; continuous gradient from 100% hex to 66%:33% hex:EtOAc over 20 min, hold at 66%:33% hex:EtOAc over 15 min) to give Part G compound as a solid (246 mg, 84%).  $[M + H]^+ = 595.5$ .

H.



Chiral cis

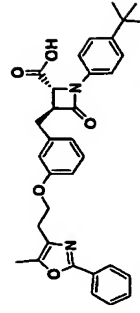
- 20 A solution of Part G compound (229 mg; 0.385 mmol) and TPA (5 mL) in  $CH_2Cl_2$  (5 mL) was stirred at RT for 4 h. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (Phenomenex reverse-phase Luna C18 5 $\mu$  30 x 250 mm column; flow rate = 20 mL/min; 30 min continuous gradient from 80:20 B:A to 100% B + 15 min hold time at 100% B, where solvent A = 90:10:0.1

$H_2O$ :MeOH:TFA and solvent B = 90:10:0.1 MeOH: $H_2O$ :TFA) to give the product, which was then chromatographed ( $SiO_2$ ; stepwise gradient from 15:1 to 10:1  $CH_2Cl_2$ :MeOH) to give Example 429 as a white solid (145 mg; 70%).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.29 (s, 9H), 2.40 (s, 3H), 3.00 (t, J = 7.9 Hz, 2H), 3.23 (dd, J = 14.5, 11.8 Hz, 1H), 3.32 (dd, J = 14.5, 3.6 Hz, 1H), 3.83-3.92 (m, 1H), 4.20-4.43 (m, 2H), 4.50 (d, J = 5.7 Hz, 1H), 6.79 (dd, J = 7.9, 2.2 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 6.96 (s, 1H), 7.20-7.35 (m, 7H), 7.40-7.46 (m, 1H), 7.92-7.98 (m, 2H);  $[M + H]^+ = 539.1$ .  $[\alpha]_D^{25} = -76.2^\circ$  (c = 0.5,  $CDCl_3$ ,  $25^\circ C$ ); Absolute stereochemistry is tentatively assigned.

- 15 Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 70:30 A:B, where A = heptane + 0.1% TFA and B = IPA+0.1% TFA; detector wavelength = 254 nm; retention time = 7.96 min; ee > 99%

20

### Example 430

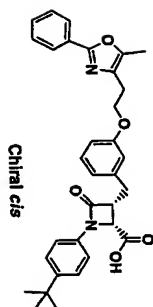


Chiral trans

- 25 During preparation of Example 429, a slower eluting side product was isolated by preparative HPLC and was determined to be the corresponding trans epimer (title compound). The epimerization was presumed to have occurred at the carboxylic acid stereocenter. Relative and absolute stereochemistry is tentatively assigned.
- 30  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.27 (s, 9H), 2.51 (s, 3H), 3.02-3.13 (m, 3H), 3.35 (dd, J = 15.9, 3.3 Hz, 1H), 3.73-3.80 (m, 1H), 3.83-3.92 (m, 1H), 4.20-4.30 (m, 2H), 6.74 (d, J = 7.7 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 6.90 (s,

1H), 7.19 (t, J = 7.7 Hz, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.50-7.61 (m, 3H), 8.05-8.09 (m, 2H); [M + H]<sup>+</sup> = 539.2.

Example 431

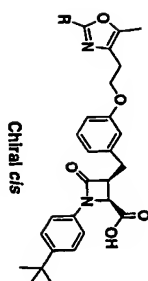





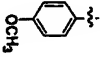
The title compound was prepared as in Example 429 by starting from Example 429 Part D compound. <sup>1</sup>H NMR: identical to Example 11; [M + H]<sup>+</sup> = 539.1; [α]<sub>D</sub><sup>20</sup> = + 62.0° (c = 0.5, CDCl<sub>3</sub>, 25°C). The absolute stereochemistry is tentatively assigned.

Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 70:30 A:B, where A = heptane + 0.1% TFA and B = isopropanol + 0.1% TFA; detector wavelength = 264 nm; retention time = 9.25 min: ee = 99.3%

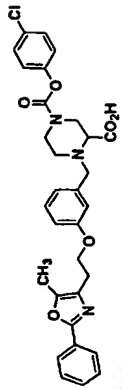
Examples 432-435

Examples 432-435 were prepared in a similar fashion to Example 429 (from Example 429, Part F compound) using a variety of 2-substituted phenyl-5-methyl oxazole-4-ethanol mesylates (prepared according to general procedure in Example 231, Part A compound) during alkylation step.

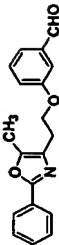


Example #	R	[M + H] <sup>+</sup>	Chiral HPLC Retention time (min)*
432		569.1	7.15
433		569.1	8.94
434		573.1	8.34
435		573.0	11.18

5 \* Chiral analytical HPLC (Daicel Chiralcel AD 4.6 x 250 mm column): flow rate = 1 mL/min; isocratic conditions = 70:30 A:B, where A = heptane + 0.1% TFA and B = isopropanol + 0.1% TFA; detector wavelength = 264 nm.

Example 436

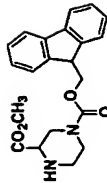
A.



5

Part A compound was prepared exactly according to the method of Example 47 Part B compound except that 3-hydroxy-benzaldehyde was used in place of 4-hydroxybenzaldehyde.

B.

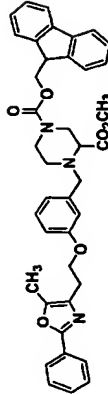


15

HCl gas was bubbled through a solution of N-1-Boc-N-4-Fmoc-2-piperazine carboxylic acid (5.0 g; 11 mmol) in MeOH (250 mL) at RT for 5 min. The reaction was stirred at RT for 5 h, then was concentrated in vacuo. The residue was partitioned between EtOAc and 1N aqueous NaOH. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part B compound (3.8 g; 95%) as an oil.

20

C.



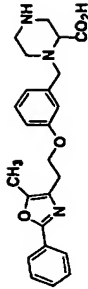
25

To a RT solution of Part B compound (1.0 g; 2.7 mmol) and Part A compound (840 mg; 2.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (150 mL) was added NaBH(OAc)<sub>3</sub> (930 mg; 4.4 mmol). The

reaction was stirred at RT for 18 h and then washed with saturated aqueous NaHCO<sub>3</sub>. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to furnish Part C compound (1.74 g; 97%) as an oil.

5

D.

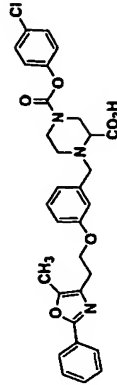


A solution of Part C compound (1.74 g; 2.65 mmol) and KOH (740 mg; 13.2 mmol) in MeOH/H<sub>2</sub>O (40 mL of a 1:1 solution) was stirred at RT for 18 h. Volatiles were removed in vacuo, and the residue was purified by preparative HPLC (YMC reverse-phase ODS 30 x 250 mm column; detection at 220 nm; flow rate = 25 mL/min; continuous gradient from 100% A to 100% B over 30 min + 10 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to provide Part D compound (510 mg; 40%) as an oil.

15

20

E.



To a RT solution of Part D compound (50 mg; 0.11 mmol) and 4-chlorophenyl chloroformate (28 mg; 0.14 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added Et<sub>3</sub>N (70  $\mu$ L; 0.52 mmol). The reaction was stirred at RT for 16 h and then was concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 100% A to 100% B over 30 min + 10 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to provide the title compound (28 mg; 44%) as a solid.

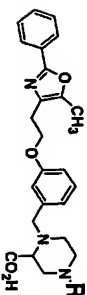
25

30

$[M + H]^+ = 577.4$

Examples 437-441

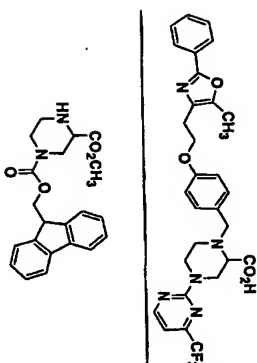
Examples 437-441 of the invention were prepared according to the general procedure described for the synthesis of Example 436.



Example #	R	$[M + H]^+$
437		560.2
438		556.2
439		600.2
440		610.2
441		592.2

Example 442

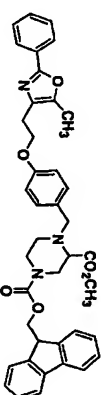
A.



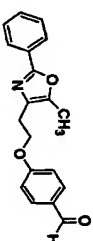
HCl gas was bubbled through a solution of N-1-Boc-N-4-Fmoc-2-piperazine carboxylic acid (2.0 g; 4.4 mmol) in MeOH (100 mL) at RT for 5 min. The reaction was stirred at RT for 3 h, then was concentrated in vacuo. The residue was partitioned between EtOAc and 1N aqueous NaOH. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part A compound (1.2 g; 75%) as an oil.

15

B.





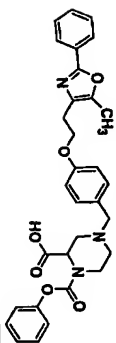
To a RT solution of Part A compound (1.1 g; 3.0 mmol) and Example 47 Part B compound (925 mg; 3.0 mmol)



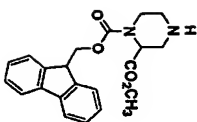
in CH<sub>2</sub>Cl<sub>2</sub> (150 mL) was added NaBH(OAc), (930 mg; 4.4 mmol) at RT. The reaction was stirred at RT for 18 h and then washed with saturated aqueous NaHCO<sub>3</sub>. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS



Example #	R	[M + H] <sup>+</sup>
444		567.6
445		500.6

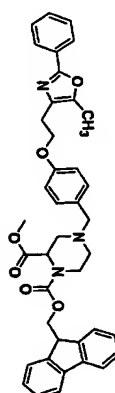
Example 446

A.



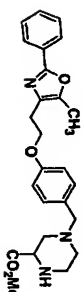
HCl gas was bubbled through a solution of N-4-Boc-N-1-Fmoc-2-piperazine carboxylic acid (1.0 g; 2.2 mmol) in MeOH (100 mL) at RT for 5 min. The reaction was stirred at RT for 2 h, then was concentrated in vacuo. The residue was partitioned between EtOAc and 1N aqueous NaOH. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part A compound (0.8g; 99%) as an oil.

B.



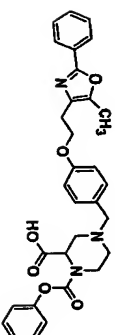
To a RT solution of Part A compound (800 mg; 2.2 mmol) and Example 47 Part B compound (670 mg; 2.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added NaBH(OAc)<sub>3</sub> (1.5 g; 7.0 mmol). The reaction was stirred at RT for 48 h and then concentrated in vacuo. The residue was partitioned between EtOAc and saturated aqueous NaHCO<sub>3</sub>. The organic phase was extracted, dried (MgSO<sub>4</sub>) and concentrated in vacuo to furnish Part B compound (1.02 g; 73%) as an oil.

C.



A solution of Part B compound (1.0 g; 1.6 mmol) and pyrrolidine (3.2 mL; 38.8 mmol) in DMF (15 mL) was stirred at RT for 18 h. Volatiles were removed in vacuo, and the residue was purified by preparative HPLC (Shimadzu VP reverse-phase ODS 20 x 250 mm column; detection at 254 nm; flow rate = 20 mL/min; continuous gradient from 90% A to 100% B over 10 min + 10 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to provide Part C compound (575 mg; 85%) as an oil.

D.



30



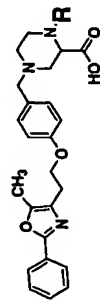
To a RT solution of Part C compound (21 mg; 0.05 mmol) and phenyl chloroformate (9.0 mg; 0.05 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added Et<sub>3</sub>N (30 μL; 0.21 mmol). The reaction was stirred at RT for 16 h and then was concentrated in vacuo. The residue was dissolved in MeOH (2.0 mL) and 2.0 mL of a 2.0M KOH solution was added. The reaction was stirred at RT for 8 h, then was concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 90% A to 100% B over 10 min + 10 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to provide the title compound (4.0 mg; 15%) as a solid. [M + H]<sup>+</sup> = 542.6

15

Examples 447-460

Examples 447-460 of the invention were prepared according to the general procedures described for the synthesis of Example 446.

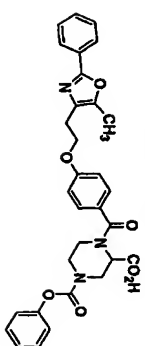
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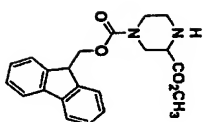
Example #	R	[M + H] <sup>+</sup>
447		494.5
448		572.6

Example #	R	[M + H] <sup>+</sup>
449		478.5
450		464.5
451		555.6
452		526.6
453		556.6
454		560.6
455		556.6
456		577

Example #	R	[M + H] <sup>+</sup>
457		572.6
458		592.6
459		542.6
460	H	422

Example 461

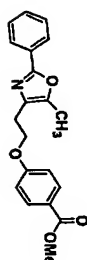
A.



- 506 -

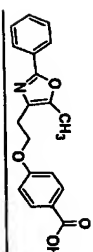
HCl gas was bubbled through a solution of N-1-Boc-N-4-Fmoc-2-piperazine carboxylic acid (4.0 g; 8.8 mmol) in MeOH (200 mL) at RT for 5 min. The reaction was stirred at RT for 2 h, then was concentrated in vacuo. The residue was partitioned between EtOAc and 1N aqueous NaOH. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part A compound (1.4 g; 42%) as an oil.

10 B.



A solution of Example 23 Part A compound (1.1 g; 3.7 mmol), 4-hydroxy-benzoic acid methyl ester (570 mg; 3.7 mmol), and K<sub>2</sub>CO<sub>3</sub> (515 mg; 3.7 mmol) in CH<sub>3</sub>CN (100 mL) was heated at 90°C with stirring for 18 h. The reaction mixture was cooled to RT, and the solvent was removed in vacuo. The residue was partitioned between EtOAc and 1 N NaOH. The organic phase was extracted, dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part B compound (1.1 g; 91%).

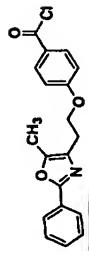
C.



A solution of Part B compound (1.1 g; 3.3 mmol) and potassium hydroxide (1.8 g; 33 mmol) in 1:1 MeOH:H<sub>2</sub>O (100 mL) was stirred at RT for 18 h. The solvent was removed in vacuo, and the residue was partitioned between EtOAc and H<sub>2</sub>O. The aqueous layer was brought to pH 5 using 1N HCl. The organic phase was extracted, dried (MgSO<sub>4</sub>) and concentrated to give Part C compound (1.1 g; >99%).

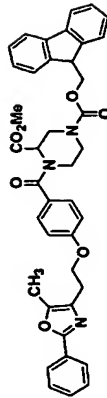
- 507 -

D.



A solution of Part C compound (1.1 g; 3.4 mmol) and oxalyl chloride (1.5 mL; 17 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was stirred at RT for 18 h. A second portion of oxalyl chloride (1.5 mL; 17 mmol) was added to the reaction, and the mixture stirred at RT for an additional 18 h. The solvent was removed in vacuo to give Part D compound (1.16 g; >99%).

E.

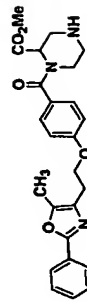


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To a RT solution of Part A compound (1.25 g mg; 3.4 mmol) and Part D compound (1.16 g; 3.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added  $\text{Et}_3\text{N}$  (1.0 mL; 6.8 mmol). The reaction was stirred at RT for 18 h and then concentrated in vacuo. The residue was partitioned between EtOAc and saturated aqueous  $\text{NaHCO}_3$ . The organic phase was extracted, dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give Part E compound (1.7 g; 75%) as an oil.

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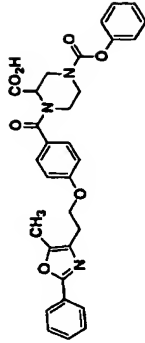
F.



A solution of Part E compound (1.7 g; 2.5 mmol) and pyrrolidine (5.2 mL; 62.5 mmol) in DMF (10 mL) was stirred at RT for 18 h. Volatiles were removed in vacuo,

and the residue was purified by preparative HPLC (Shimadzu VP reverse-phase ODS 20 x 250 mm column; detection at 254 nm; flow rate = 20 mL/min; continuous gradient from 90:10 A:B to 100% B over 10 min + 10 min hold time at 100% B, where A = 90:10:0.1  $\text{H}_2\text{O}$ :MeOH:TFA and B = 90:10:0.1 MeOH: $\text{H}_2\text{O}$ :TFA) to provide Part F compound (1.08 g; 96%) as an oil.

G.



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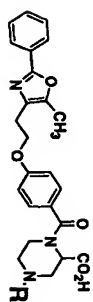
To a RT solution of Part F compound (50 mg; 0.11 mmol) and phenyl chloroformate (21 mg; 0.13 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added  $\text{Et}_3\text{N}$  (70  $\mu\text{L}$ ; 0.48 mmol). The reaction was stirred at RT for 16 h and then was concentrated in vacuo. The residue was dissolved in MeOH (2.0 mL) and aqueous KOH (2.0 mL of a 2 M solution) was added. The reaction stirred at RT for 8 h and then was concentrated in vacuo. The residue was purified by preparative HPLC (exactly as described in Part F) to provide the title compound (10.0 mg; 16%) as a solid.  $[\text{M} + \text{H}]^+ = 556.6$

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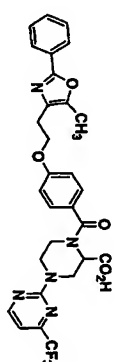
# Examples 462-468

Examples 462-468 of the invention were prepared according to the general procedures described for the synthesis of Example 461.

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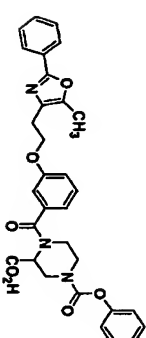


Example No.	R	[M + H] <sup>+</sup>
462		586.6
463		536.6
464		478.5
465		507.6
466		555.6
467		569.6
468		540.6

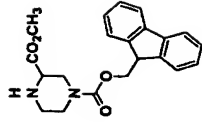
Example 469

To a RT solution of Example 461 Part F compound (50 mg; 0.11 mmol) and 2-chloro-4-(trifluoromethyl)pyrimidine (21 mg; 0.11 mmol) in CH<sub>3</sub>CN (2 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (37 mg; 0.11 mmol). The reaction was stirred at RT for 16 h, then at 60°C for 4 h and then was concentrated in vacuo. The residue was dissolved in MeOH (2.0 mL) and aqueous KOH (2.0 mL of a 2.0M solution) was added. The reaction was stirred at 60°C for 18 h and was concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 90% A to 100% B over 10 min + 10 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to provide the title compound (5.0 mg; 10%) as a solid.

[M + H]<sup>+</sup> = 582.5

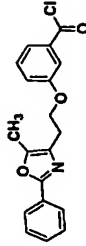
Example 470

A.



HCl gas was bubbled through a solution of N-1-Boc-N-4-Emoc-2-piperazine carboxylic acid (4.0 g; 8.8 mmol) in MeOH (200 mL) at RT for 5 min. The reaction was stirred at RT for 2 h, then was concentrated in vacuo. The residue was partitioned between EtOAc and 1N aqueous NaOH. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part A compound (1.4 g; 42%) as an oil.

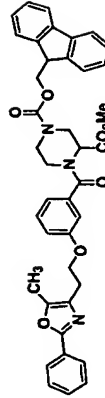
B.



Part B compound was prepared according to the procedure described for the synthesis of Example 461

Parts B-D compounds, except that 3-hydroxy-benzoic acid methyl ester was used in place of 4-hydroxy-benzoic acid methyl ester.

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A RT solution of Part A compound (1.25 g mg; 3.4 mmol), Part B compound (1.16 g; 3.4 mmol) and Et<sub>3</sub>N (1.0 mL; 6.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was stirred at RT for 18 h and then concentrated in vacuo. The residue was

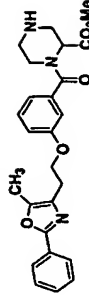
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PCT/US2003/022149

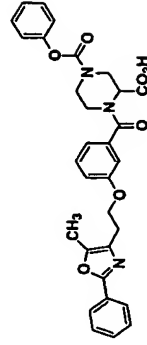
partitioned between EtOAc and saturated aqueous  $\text{NaHCO}_3$ . The organic phase was extracted, dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to furnish Part C compound (2.2 g; 99%) as an oil.

८



A solution of Part C compound (2.2 g; 3.3 mmol) and pyrrolidine (6.8 mL; 82.0 mmol) in DMF (10 mL) was stirred at RT for 18 h. Volatiles were removed in vacuo and the residue was purified by preparative HPLC (Shimadzu VP reverse-phase ODS 20 x 250 mm column; detection at 254 nm; flow rate = 20 mL/min; continuous gradient from 90% A to 100% B over 10 min + 10 min hold time at 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to provide Part D compound (382 mg; 26%) as an oil.

20 E.

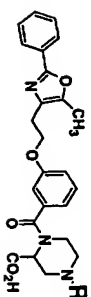


To a RT solution of Part D compound (40 mg; 0.09 mmol) and phenyl chloroformate (17 mg; 0.11 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added  $\text{Et}_3\text{N}$  (60  $\mu\text{L}$ ; 0.39 mmol). The reaction was stirred at RT for 16 h and then was concentrated in vacuo. The residue was dissolved in methanol (2.0 mL) and aqueous KOH (2.0 mL of a 2 M solution) was added. The reaction was stirred at RT 8 h and was concentrated in vacuo. The residue was purified by preparative HPLC (as described for Part D

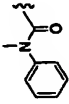


compound) to provide the title compound (11.0 mg; 22%) as a solid.  $[M + H]^+ = 556.6$

### Examples 471-477

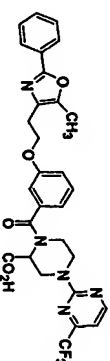
Examples 471-477 of the invention were prepared according to the general procedures described for the synthesis of Example 470.



Example #	R	[M + H] <sup>+</sup>
471		586.6
472		536.6
473		507.6
474		555.6

Example #	R	[M + H] <sup>+</sup>
475		569.6
476		540.6
477		478.5

### Example 478

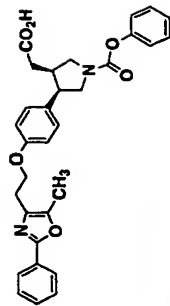


To a RT solution of Example 470 Part D compound (40 mg; 0.09 mmol) and 2-chloro-4-(trifluoromethyl)pyrimidine (17 mg; 0.09 mmol) in CH<sub>3</sub>CN (2 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (30 mg; 0.09 mmol). The reaction was stirred at RT for 18 h and then was concentrated in vacuo. The residue was dissolved in methanol (2.0 mL) and aqueous KOH (2.0 mL of a 2 M solution) was added. The reaction was stirred at RT for 18 h and was concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; detection at 220 nm; flow rate = 20 mL/min; continuous gradient from 90% A to 100% B over 10 min + 10 min hold time at 100% B, where A = 90:10:0.1

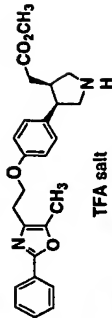
H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to provide the title compound (3.0 mg; 6%) as a solid.  $[M + H]^+ = 582.5$

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### Example 479



A.

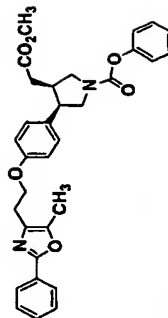


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A solution of Example 242 Part A compound (65.6 mg; 0.126 mmol) in TFA (1 mL) and CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was stirred at RT for 1.5 h, then was concentrated in vacuo to give Part A compound as an oil (66 mg), which was used in the next step without further purification.

15

B.



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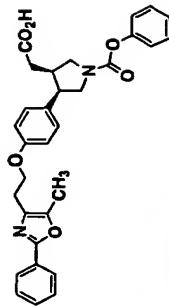
To a solution of Part A compound (9.4 mg, 0.0176 mmol) and NaHCO<sub>3</sub> (15 mg; 0.178 mmol) in H<sub>2</sub>O (0.7 mL) and THF (1 mL) was added phenyl chloroformate (15 mg, 0.0285

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mmol). The reaction was stirred at RT for 2 h, then was partitioned between EtOAc and H<sub>2</sub>O (1 mL each). The organic phase was concentrated in vacuo to give Part B compound as an oil.

5

C.



10

A mixture of Part B compound and LiOH·H<sub>2</sub>O (8 mg; 0.19 mmol) in THF/H<sub>2</sub>O (1 mL of a 1:1 solution) was stirred at RT for 16 h, after which the pH was adjusted to ~5 with aqueous 1 M HCl. The mixture was extracted with EtOAc (2 mL). The combined organic extracts were concentrated in vacuo and the residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; flow rate = 20 mL/min; 10 min continuous gradient from 30:70 B:A to 100% B + 5 min hold-time at 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give the title compound (5.0 mg; 54%).  $[M + H]^+ = 527.0$

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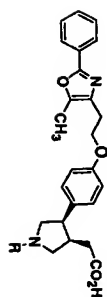
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### Examples 480-486

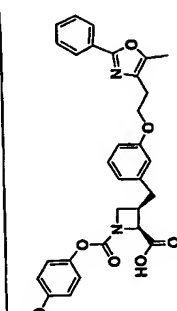
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Examples 480-486 of the invention were prepared in a similar fashion to the synthesis of Example 479 (from Example 479 Part A compound) using a variety of chloroformates.

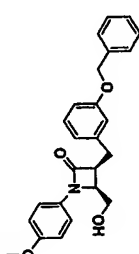
30



Example #	R	[M + H] <sup>+</sup>
480		479.1
481		493.1
482		493.1
483		507.1
484		539.0
485		541.0
486		557.0

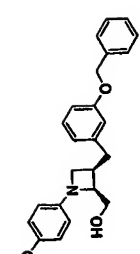
Example 487.

## A.



5 To a solution of Example 419 Part F compound (2.0 g, 4.99 mmol) in THF (60 mL) was added LiBH<sub>4</sub> (0.18 g 8.26 mmol) and MeOH (6 mL). The reaction was stirred at RT for 2 h. Volatiles were removed in vacuo and the residue was partitioned between saturated aqueous NaHCO<sub>3</sub> (20 mL) and EtOAc (250 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; continuous gradient from 92:8 hex:EtOAc to 65:35 hex:EtOAc over 40 min, 65:35 hex:EtOAc for 20 min) to give Part A compound (1.5 g, 75%) as a solid.

## B.



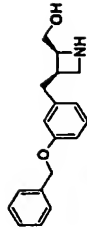
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Monochloro-alane was prepared according to the literature procedure (Ref: Benito Alcalde et al, JOC



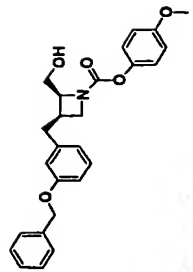
1999, 64, 9596). A solution of anhydrous  $\text{AlCl}_3$  (400 mg, 3.1 mmol) in dry  $\text{Et}_2\text{O}$  (5 mL) was added to a well-stirred suspension of  $\text{LiAlH}_4$  (118 mg, 1.73 mmol) in anhydrous  $\text{Et}_2\text{O}$ . The mixture was heated at reflux for 30 min and cooled to RT. An aliquot of this monochloro-alane solution in  $\text{Et}_2\text{O}$  (10 mL, ~3.1 mmol) was transferred via cannula into a solution of Part A compound (0.7 g, 1.73 mmol) in THF (21 mL) at RT. The mixture was stirred at RT for 1.5 h, then was partitioned between water (5 mL) and EtOAc (150 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo; the residue was chromatographed ( $\text{SiO}_2$ ; 3:2 hex:EtOAc) to give Part B compound (0.38 g; 56 %) as a colorless oil.  $[\text{M} + \text{H}]^+ = 390.3$ .

C.



To a 0°C solution of Part B compound (0.2 g; 0.52 mmol) in  $\text{CH}_3\text{CN}$  (3 mL) was added aqueous ceric ammonium nitrate (0.422 g in 2.1 mL  $\text{H}_2\text{O}$ ; 0.77 mmol). The reaction was stirred at 0°C for 30 min, then was partitioned between EtOAc (10 mL) and saturated aqueous sodium sulfite (5 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give crude Part C compound as an oil.

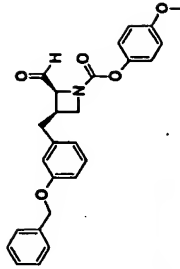
D.



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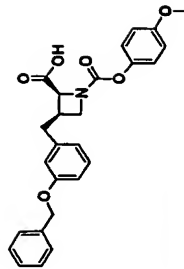
To a solution of Part C compound in THF (3 mL) was added aqueous  $\text{NaHCO}_3$  (0.128 g in 2 mL  $\text{H}_2\text{O}$ ; 1.52 mmol) and 4-methoxyphenyl chloroformate (0.1 mL, 0.67 mmol). The reaction mixture was stirred at RT for 30 min, then was partitioned between water (5 mL) and EtOAc (20 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo; the residue was chromatographed ( $\text{SiO}_2$ ; stepwise gradient from 2:1 to 1.5:1 hex:EtOAc) to give Part D compound (31.2 mg; 14% over 2 steps) as a colorless oil.  $[\text{M} + \text{H}]^+ = 434.3$ .

E.



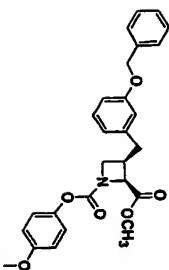
To a mixture of Dess-Martin periodinane (58 mg; 0.137 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) at RT was added a solution of Part D compound (40 mg; 0.093 mmol). The reaction was stirred at RT for 30 h. Volatiles were removed in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; 2:1 hex:EtOAc) to give Part E compound as an oil.

F.

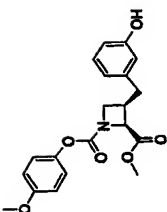


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To a 0°C solution of Part E compound in acetone (2 mL) was added Jones reagent (~3 drops). The reaction was stirred at RT for 30 min. Volatiles were removed in vacuo and the residue was partitioned between water (2 mL) and EtOAc (5 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to give crude Part F compound, which was used in the next step without further purification. [M + H]<sup>+</sup> = 448.3.



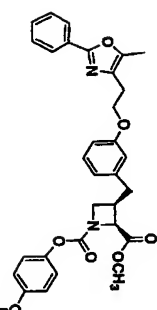
To a 0°C solution of Part F compound in MeOH (1.5 mL) and CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) was added TMSCHN<sub>2</sub> (0.2 mL of a 2M solution in hexane; 0.4 mmol). The reaction was stirred at RT for 2 h. Volatiles were moved in vacuo. The residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from 3:1 to 2:1 hex:EtOAc) to give Part G compound (30 mg; 70% over two steps) as an oil. [M + H]<sup>+</sup> = 462.3



A mixture of Part G compound (30 mg; 0.065 mmol) and 10% Pd/C (8 mg) in EtOAc (3.5 mL) was stirred under

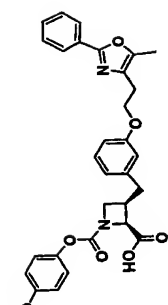
an atmosphere of H<sub>2</sub> (balloon) at RT for 4 h, at which point the reaction was complete by HPLC. The catalyst was filtered off through Celite® and the filtrate was concentrated in vacuo to give crude Part H compound (17.0 mg, 71 %) as a white solid which was used in the next step without further purification. [M + H]<sup>+</sup> = 372.6.

I.



A mixture of Part H compound (17 mg; 0.045 mmol), Example 23 Part A compound (23 mg; 0.082 mmol) and powdered K<sub>2</sub>CO<sub>3</sub> (16 mg; 0.115 mmol) in CH<sub>3</sub>CN (2 mL) was stirred at 90°C for 4 h, after which another portion of Example 23 Part A compound (20 mg; 0.082 mmol) was added. The reaction mixture was stirred at 90°C for another 14 h, cooled to RT and filtered. The filtrate was concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from 3:1 to 1:1 hex:EtOAc) to give Part I compound as an oil.

J.

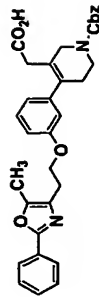


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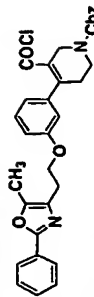
A solution of Part I compound and aqueous LiOH (4 mg in 0.6 mL H<sub>2</sub>O, 0.095 mmol) in THF (1.5 mL) was stirred at RT for 6 h, then acidified to pH 4 by the addition of 1M aqueous HCl. Volatiles were removed in vacuo and the residue was partitioned between water (2 mL) and EtOAc (10 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (continuous gradient from 70:30 A:B to 100%B; A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA; B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA; 12 min run @ 20 mL/min; detection at 220 nm; YMC ODS 20 x 100 mm column) to give the title compound (4.0 mg; 16 %) as a viscous oil.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 2.28(3H, s), 2.55-2.65 (1H, m), 2.89-2.90 (3H, m), 3.2-3.3 (1H, m), 3.69 (3H, s), 3.70-4.10 (2H, m), 4.14 (2H, t, J = 6.6 Hz), 4.70-4.90 (1H, m), 6.60-7.10 (m, 8H), 7.35-7.40 (3H, m), 7.80-7.90 (2H, m) [M + H]<sup>+</sup> = 543.2

#### Example 488

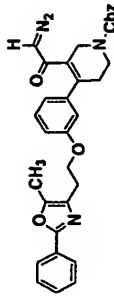


A.



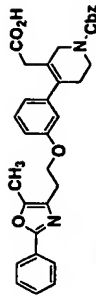
To a solution of crude Example 310 (~100 mg) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added oxalyl chloride (1.4 mL of a 1 mL solution in CH<sub>2</sub>Cl<sub>2</sub>; 1.4 mmol) and one drop of DMF. The solution was stirred for 18 h at RT and then concentrated in vacuo to give Part A compound.

B.



To a solution of diazomethane in 20 mL of Et<sub>2</sub>O (prepared from 10 mL of 50% aqueous KOH and 1-methyl-3-nitro-1-nitrosoguanidine (0.411 g; 2.8 mmol) in 20 mL of Et<sub>2</sub>O at 0 °C according to the procedure described in Example 281 Part C), was added a solution of Part A compound in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and Et<sub>2</sub>O (10 mL). The solution was stirred for 4 h at RT and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 4:1 hex:EtOAc) to give Part B compound.

C.



To a solution of Part B compound in MeOH (5 mL) was added silver benzoate (64 mg; 0.28 mmol) and Et<sub>3</sub>N (0.2 mL) at RT. The mixture was stirred at RT for 4 h and then filtered. Aqueous 1 N KOH (2 mL) was added to the filtrate and the mixture was stirred for 3 h at RT, then was neutralized with 1 N HCl, concentrated in vacuo and partitioned between brine and EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was purified by HPLC (YMC reverse-phase ODS 20 x 100 mm column; flow rate = 20 mL/min; 10 min continuous gradient from 30:70 B:A to 100% B + 5 min hold-time at 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give the title compound (7 mg; 7%).

[M + H]<sup>+</sup> = 553.2



arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl,  
 heteroarylsulfonyl, arylsulfonyl, alkoxyarylalkyl,  
 heteroarylalkoxycarbonyl, arylheteroarylalkyl,  
 alkoxyarylcarbonyl, aryloxyheteroarylalkyl,  
 5 heteroarylalkyloxyarylalkyl, arylarylalkyl,  
 arylalkenylarylalkyl, arylalkoxyarylalkyl,  
 arylcarbonylarylalkyl, alkylaryloxyarylalkyl,  
 arylalkoxycarbonylheteroarylalkyl, heteroarylalkyl,  
 arylcarbonylheteroarylalkyl, heteroaryloxyarylalkyl,  
 10 arylalkenylheteroarylalkyl, arylaminoarylalkyl,  
 aminocarbonylarylalkyl;

E is CH or N;

Z is  $(CH_2)_x^5$  where  $x^5$  is 0 (a single or a double  
 bond), 1 or 2, or Z is  $(CH_2)_x^6$  where  $x^6$  is 2 to 5, where  
 15  $(CH_2)_x^6$  includes an alkenyl (C=C) bond embedded within the  
 chain or Z is  $-(CH_2)_x^7-O-(CH_2)_x^8-$  where  $x^7$  is 0 to 4 and  $x^8$   
 is 0 to 4;

$(CH_2)_x^1$ ,  $(CH_2)_x^2$ ,  $(CH_2)_x^3$ ,  $(CH_2)_x^4$ ,  $(CH_2)_x^5$ ,  
 $(CH_2)_x^6$ ,  $(CH_2)_x^7$ ,  $(CH_2)_x^8$ ,  $(CH_2)_n$ ,  $(CH_2)_p$  and  $(CH_2)_q$   
 20 may be optionally substituted;

Y is  $CO_2R^4$  where  $R^4$  is H or alkyl, or a prodrug  
 ester, or Y is a C-linked 1-tetrazole, a phosphinic acid  
 of the structure  $P(O)(OR^{4a})R^5$  where  $R^{4a}$  is H or a prodrug  
 ester,  $R^5$  is alkyl or aryl, or a phosphonic acid of the  
 25 structure  $P(O)(OR^{4a})_2$ ;

including all stereoisomers thereof, prodrug esters  
 thereof, and pharmaceutically acceptable salts thereof.

2. The compound as defined in Claim 1 wherein X is  
 30 CH.

3. The compound as defined in Claim 1 wherein A is  
 $-(CH_2)_x^2-O-$ .

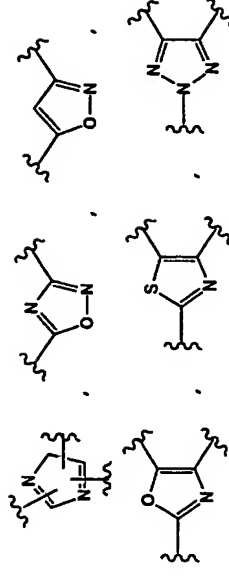
4. The compound as defined in Claim 1 wherein Q is  
 C.  
 5. The compound as defined in Claim 1 wherein B is  
 a bond.

5

6. The compound as defined in Claim 1 wherein

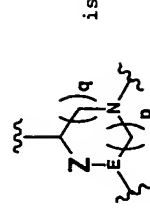


is



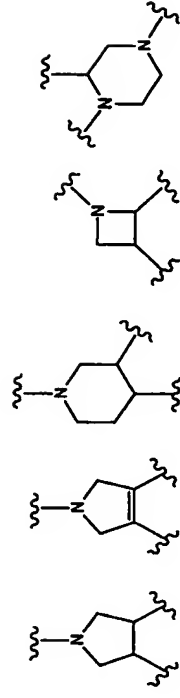
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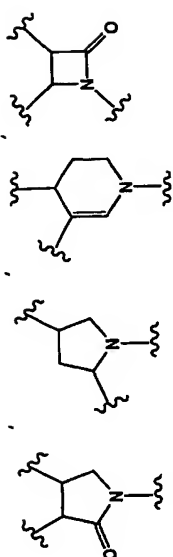
7. The compound as defined in Claim 1 wherein



is

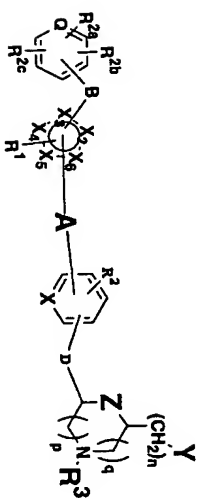
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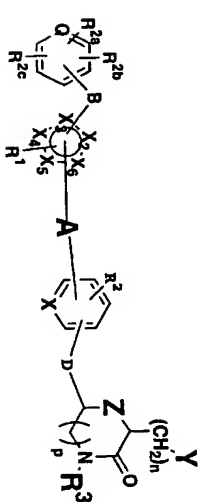


8. The compound as defined in Claim 1 having the  
5 structures

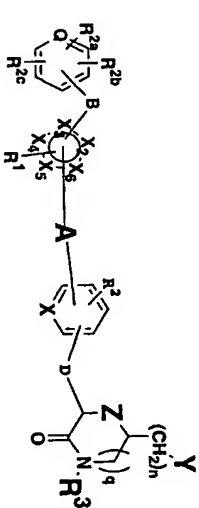
Ia



10 Ib



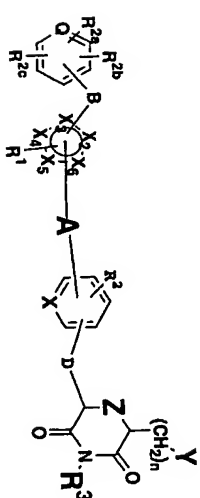
Ic



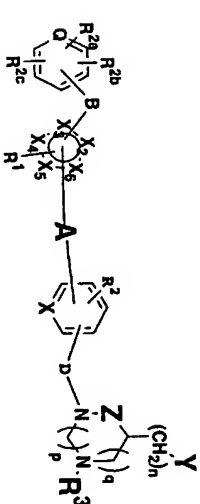
15

Id

- 530 -

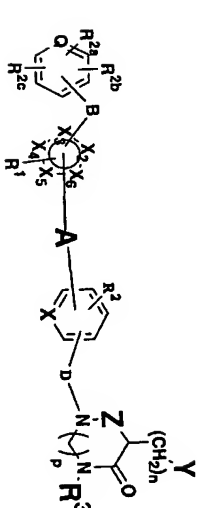


Ie

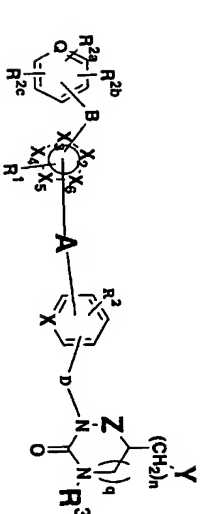


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If

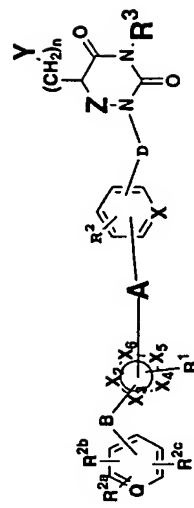


10 Ig



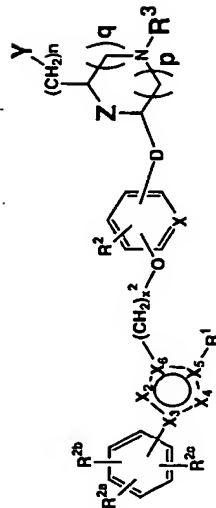
Ih

- 531 -



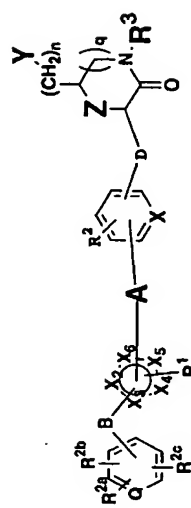
9. The compound as defined in Claim 1 having the structure

5



where X is CH.

10 IB



where X is CH.

11. The compound as defined in Claim 1 having the structure

15

wherein

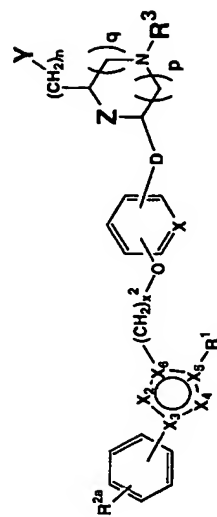
R<sup>1</sup> is alkyl;

R<sup>2a</sup> is alkyl, alkoxy or halogen;

X<sup>2</sup> is 1 to 3;

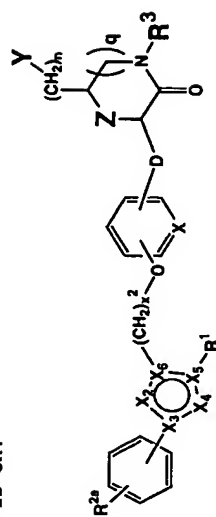
D is -CH= or (CH<sub>2</sub>)<sub>m</sub>, where m is 0 or (CH<sub>2</sub>)<sub>m</sub> is CH<sub>2</sub> or CH-alkyl;

X is CH;



where X is CH.

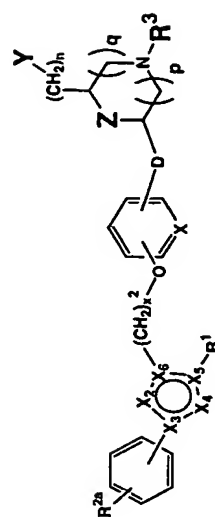
5



where X is CH, q = 0, and Z is a single bond.

11. The compound as defined in Claim 1 having the structure

10



wherein

R<sup>1</sup> is alkyl;

R<sup>2a</sup> is alkyl, alkoxy or halogen;

X<sup>2</sup> is 1 to 3;

D is -CH= or (CH<sub>2</sub>)<sub>m</sub>, where m is 0 or (CH<sub>2</sub>)<sub>m</sub> is CH<sub>2</sub> or CH-alkyl;

X is CH;

$X_1, X_2, X_3, X_4$  and  $X_5$  represent a total of 1, 2 or 3 nitrogens;

$(CH_2)_n$  is a bond or  $CH_2$ ;

$p$  is 1;

$z$  is a bond;

$q$  is 1;

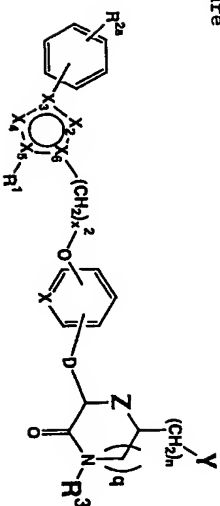
$R^1$  is alkoxy, carbonyl, aryl, heteroaryl,

aryloxy, carbonyl or arylalkyl;

$Y$  is  $CO_2R^1$ ; and

$n$  is 0.

12. The compound as defined in Claim 1 having the structure



15 wherein  $R^1$  is alkyl;

$R^2$  is alkyl, alkoxy or halogen,

$x^1$  is 1 to 3;

$D$  is  $-CH=$  or  $(CH_2)_m$  where  $m$  is 0 or  $(CH_2)_n$  is  $CH_2$  or

20  $CH-alkyl$ ;

$X$  is  $CH$ ;

$X_1, X_2, X_3, X_4$  and  $X_5$  represent a total of 1, 2 or 3

nitrogens;

$(CH_2)_n$  is a bond or  $CH_2$ ;

25  $Z$  is a bond,

$q$  is 0 or 1;

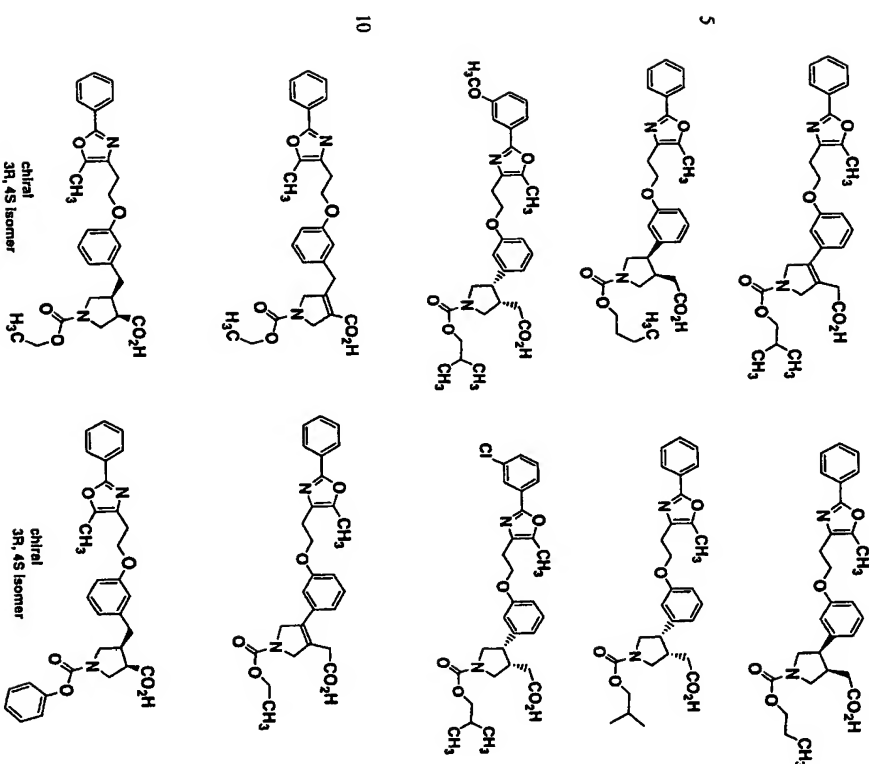
$R^1$  is alkoxy, carbonyl, aryl, heteroaryl,

aryloxy, carbonyl or arylalkyl;

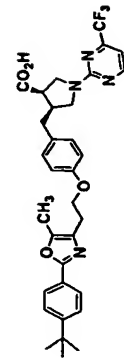
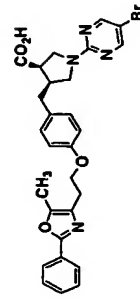
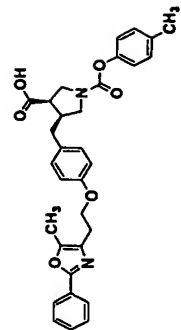
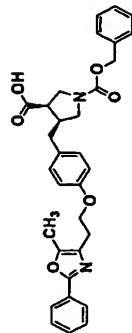
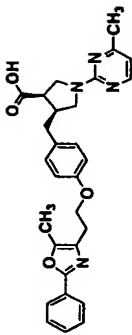
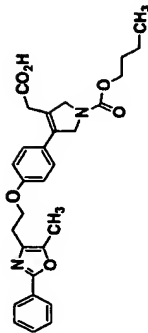
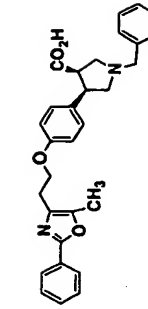
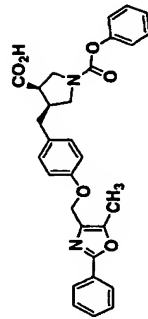
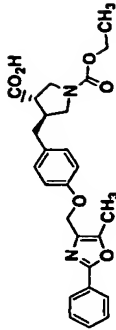
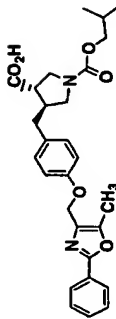
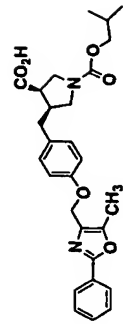
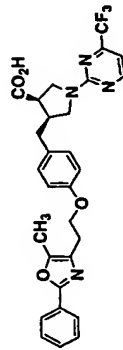
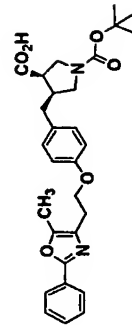
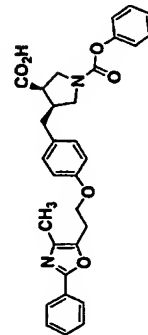
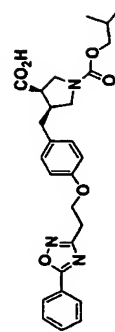
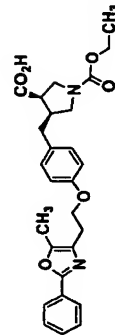
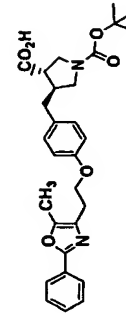
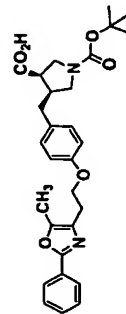
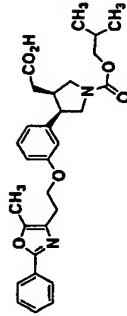
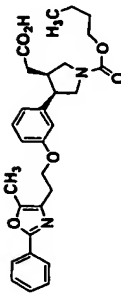
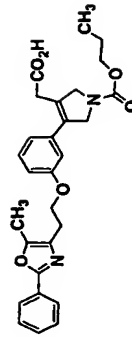
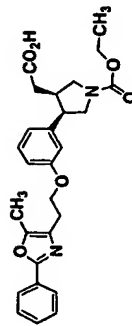
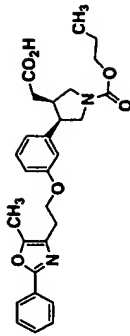
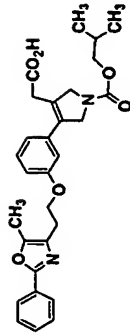
$Y$  is  $CO_2R^1$ ; and

30  $n$  is 0.

13. The compound as defined in Claim 1 having the structure





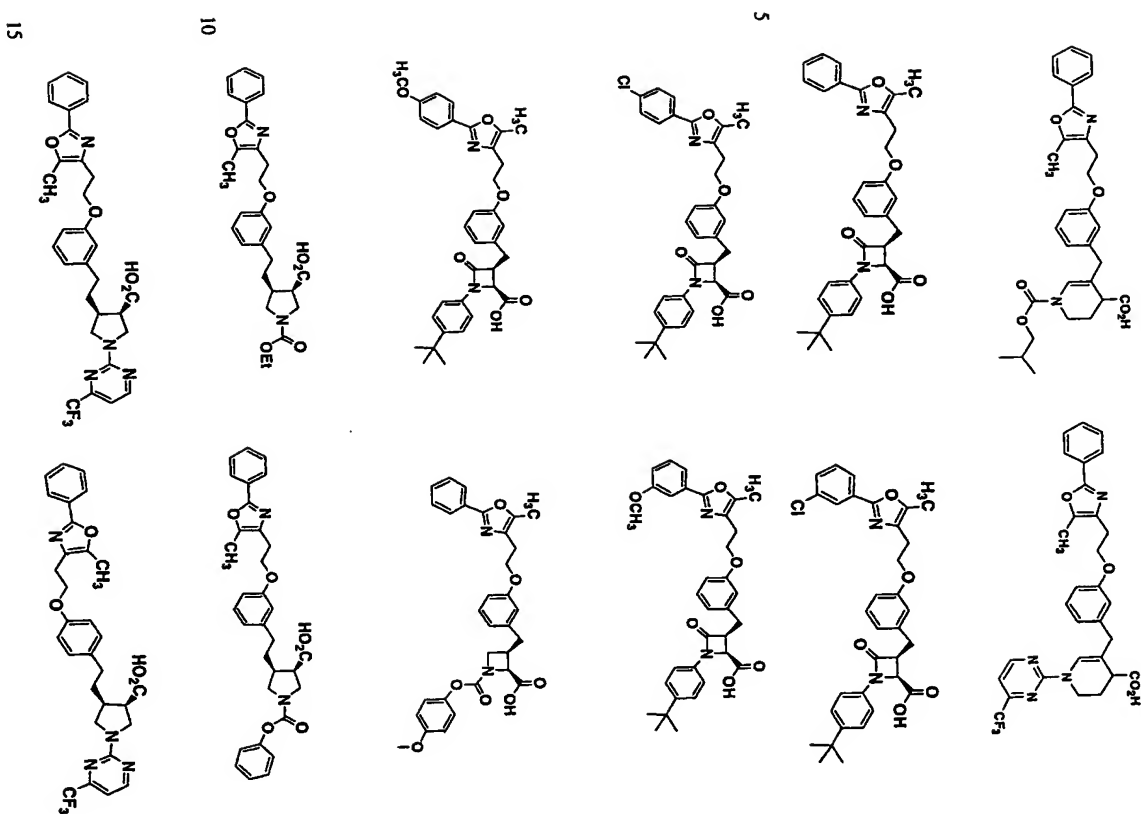
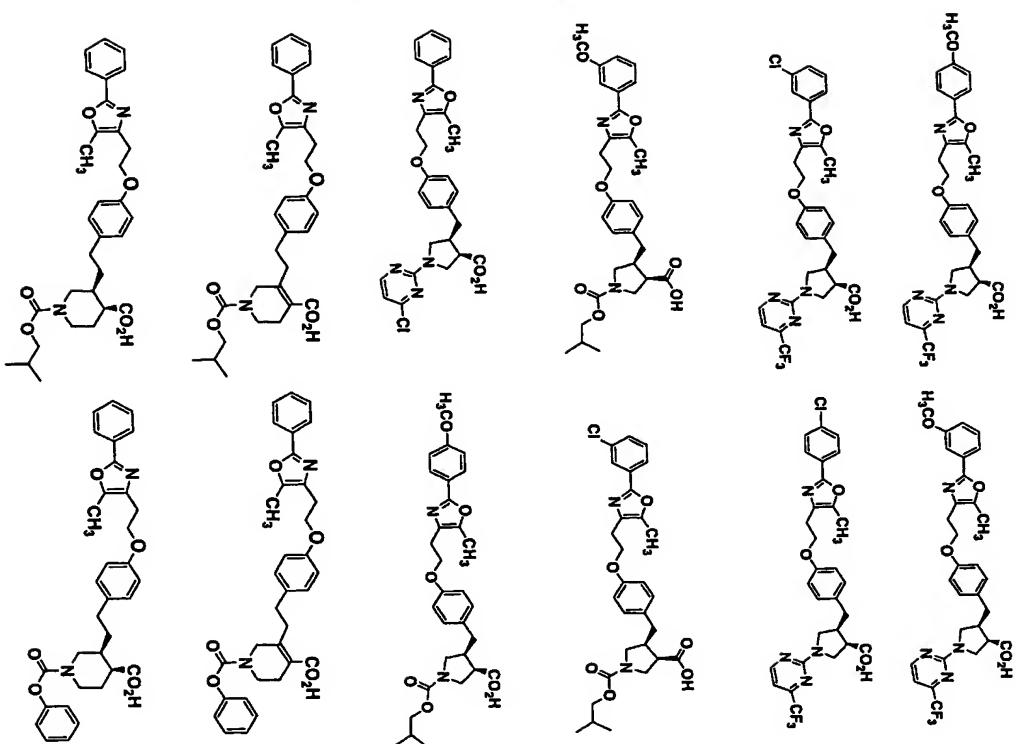


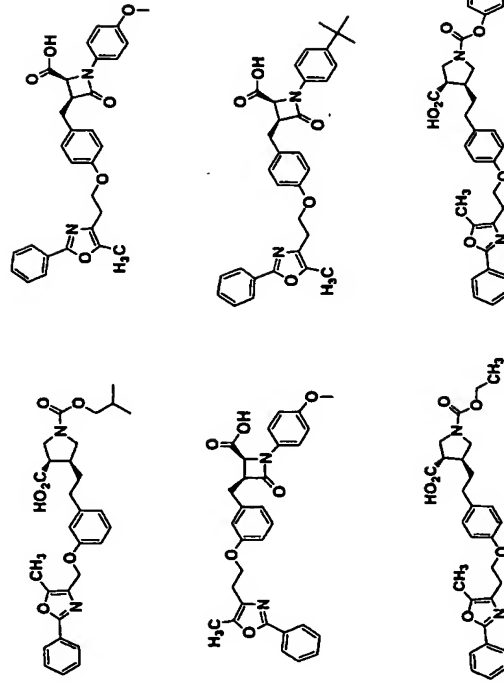
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14. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

15. A method for treating diabetes, especially Type 2 diabetes, and related diseases such as insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, inflammation, Syndrome X, diabetic complications, dysmetabolic syndrome, atherosclerosis, and related diseases, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

20

16. A method for treating early malignant lesions (such as ductal carcinoma in situ of the breast and lobular carcinoma in situ of the breast), premalignant lesions (including fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN), liposarcomas

25

and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and osteoporosis and proliferative diseases such as

5 psoriasis, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

17. A pharmaceutical combination comprising a compound as defined in Claim 1 and a lipid-lowering agent, a lipid modulating agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor, and/or an antiosteoporosis agent.

10

18. The combination as defined in Claim 17 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR  $\gamma$  agonist, a PPAR  $\alpha/\gamma$  dual agonist, an SGLT2 inhibitor, a

15

20 DP4 inhibitor, an  $\alpha\text{P2}$  inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1), insulin and/or a meglitinide, the anti-obesity agent is a beta 3

adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an  $\alpha\text{P2}$  inhibitor, a cannabinoid receptor-1 antagonist and/or an anorectic agent, the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxxygenase

25

30 inhibitor, a farnesoid receptor (FXR) agonist, a liver X receptor (LXR) agonist, a CETP inhibitor or an ACAT inhibitor, the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE

inhibitor, calcium channel blocker and/or  $\beta$ -adrenergic blocker.

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19. The combination as defined in Claim 18 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipizide, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, rosiglitazone, balaglitazone, insulin, G1-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-H039242, GW-409544, KRP297, AZ-242, AC2993, LY315902, P32/98 and/or NVP-DPP-728A, the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropionylamine, rimonabant (SR-141716) and/or mazindol, the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, itavastatin, visastatin, rosuvastatin, pitavastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, ezetimibe, TS-962, MD-700, cholesteryl, niacin and/or LY295427, the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentanyl, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S((R\*,R\*))]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440;
- 20 an angiotensin II receptor antagonist which is 25 an angiotensin II receptor antagonist which is irbesartan, losartan, telmisartan or valsartan; amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl, the platelet aggregation inhibitor is 30 aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban.